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ADVANCED PARAMETERISATION OF ONLINE HANDWRITING IN WRITERS WITH GRAPHOMOTOR DISABILITIES
POKROČILÉ METODY PARAMETRIZACE ONLINE PÍSMA OSOB S GRAFOMOTORICKÝMI OBTÍŽEMI

DOCTORAL THESIS
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ABSTRACT

Graphomotor disabilities (GD) significantly affect the quality of life beginning from the school-age, when the graphomotor skills are developed, until the elderly age. The timely diagnosis of these difficulties and therapeutic interventions are of great importance. As GD are associated with several symptoms in the field of kinematics, the basic kinematic features such as velocity, acceleration, and jerk were proved to effectively quantify these symptoms. Nevertheless, an objective computerized decision support system for the identification and assessment of GD is still missing. Therefore, the main objective of my dissertation is the research of an advanced online handwriting parametrization utilized in the field of GD analysis, with a special focus on methods based on fractional calculus. This work is the first to experiment with fractional-order derivatives (FD) in the GD analysis by online handwriting of Parkinson's disease (PD) patients and school-age children. A new online handwriting parametrization technique based on the Grünwald-Letnikov approach of FD has been proposed and evaluated. In the field of PD dysgraphia, a significant improvement in the discrimination power and descriptive abilities was proven. Similarly, the proposed methodology improved current state-of-the-art techniques of GD analysis in school-aged children. The newly designed parametrization has been optimized in the scope of the computational performance (up to 80 %) as well as in FD order fine-tuning. Finally, various FD-approaches were compared, namely Riemann-Liouville, Caputo's, together with Grünwald-Letnikov approximation to identify the most suitable approach for particular areas of GD analysis.

KEYWORDS

advanced parametrization, fractional calculus, fractional order derivatives, graphomotor disabilities, online handwriting

ABSTRAKT

Grafomotorické obtíže (GD) výrazně ovlivňují kvalitu života školním věkem počínajíc, kde se vyvíjejí grafomotorické schopnosti, až do důchodového věku. Včasná diagnóza těchto obtíží a terapeutický zásah mají velký význam k jejich zlepšení. Vzhledem k tomu, že GD souvisí z vícerými symptomy v oblasti kinematiky, základní kinematické parametry jako rychlost, zrychlení a švih prokázaly efektivní kvantizaci těchto symptomů. Objektivní výpočetní systém podpory rozhodování pro identifikaci a vyšetření GD však není dostupný. A proto je hlavním cílem mé disertační práce výzkum pokročilé metody parametrizace online písma pro analýzu GD se speciálním zaměřením na využití metod zlomkového kalkulu. Tato práce je první, která experimentuje s využitím derivací neceločíselného řádu (FD) pro analýzu GD pomocí online písma získaného od pacientů s Parkinsonovou nemocí a u dětí školního věku. Byla navržena a evaluována nová metoda parametrizace online písma založena na FD využitím Grünwald-Letnikova přístupu. Bylo dokázáno, že navržená metoda významně zlepšuje diskriminační sílu a deskriptivní schopnosti v oblasti Parkinsonické dysgrafie. Stejně tak metoda pozitivně ovlivnila i nejmodernější techniky v oblasti analýzy GD u dětí školního věku. Vyvinutá parametrizace byla optimalizována s ohledem na výpočetní náročnost (až o 80 %) a také na vyladění řádu FD. Ke konci práce byly porovnány víceré přístupy výpočtu FD, jmenovitě Riemann-Liouvillův, Caputův společně z Grünwald-Letnikovým přístupem za účelem identifikace těch nejvhodnějších pro jednotlivé oblasti analýzy GD.

KLÍČOVÁ SLOVA

pokročilá parametrizace, zlomkový kalkulus, derivace libovolným řádem, grafomotorické obtíže, online písmo

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DECLARATION

I declare that I have written the Doctoral Thesis titled "Advanced parameterisation of online handwriting in writers with graphomotor disabilities" independently, under the guidance of the advisor and using exclusively the technical references and other sources of information cited in the thesis and listed in the comprehensive bibliography at the end of the thesis.

As the author I furthermore declare that, with respect to the creation of this Doctoral Thesis, I have not infringed any copyright or violated anyone's personal and/or ownership rights. In this context, I am fully aware of the consequences of breaking Regulation § 11 of the Copyright Act No. 121/2000 Coll. of the Czech Republic, as amended, and of any breach of rights related to intellectual property or introduced within amendments to relevant Acts such as the Intellectual Property Act or the Criminal Code, Act No. 40/2009 Coll., Section 2, Head VI, Part 4.

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DEDICATION

I dedicate this work to all who like to overcome themselves and are not afraid to explore the unconventional spaces of science.

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I would like to express my gratitude to my beloved wife Johanka, who supports me during the most difficult moments in my scientific career, and who gives me the light in my life together with my son Janko. Thank you.

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Preamble

1 Introduction

The universe of science is indescribable by simple words or short thoughts. Our life is not long enough to fully understand what nature can provide. Still, our role as scientists is to uncover the mysteries around us and use them to create a better environment for all living beings. And this is what drives me through the pitfalls of the research. To help people live a dignified life.

Four years of my work in the field of advanced biomedical signal processing culminates in this document in the form of the cumulative dissertation. It comprises all of the published studies produced by me and my co-authors in this area. A brief introduction to relevant topics is given, and the genesis of the proposed methodology is described. The particular papers are summarized and contextually linked into a storyline. The work as a whole is discussed and concluded, and additionally, further directions are stated.

The main idea of my research is to help people with graphomotor disabilities (Parkinson's disease patients and school-aged children) to improve the quality of life by early identification and proper description of the handwriting disturbances. The primary objective is to propose an advanced online handwriting parametrization utilized in the field of graphomotor disabilities analysis, with a special focus on methods based on fractional calculus.

This thesis is structured into three main parts, namely the Preamble, Publications, and Appendix. In the following sections, the relevant topics are briefly introduced, namely the fractional calculus and online handwriting in people with handwriting difficulties together with objectives of this thesis. A more experienced reader with sufficient background in fractional order derivatives and handwritten signal processing may consider skipping the Introduction section and continuing directly to Summary of the Publications. In the Concluding Discussion section, the particular aims of this thesis are addressed.

1.1 Fractional Calculus

The theory of the Fractional Calculus (FC) – the derivative and integral of an arbitrary real order – goes back to the Leibniz's note discussing the derivative of order one half in his list to L'Hospital dated 30 September 1695. Since then, the theory of fractional order derivatives (FD) has been developed as a pure theoretical field of mathematics for centuries. It attracted the interest of many famous mathematicians, including Euler, Liouville, Laplace, Riemann, Grünwald, or Letnikov. Nevertheless, in the last few decades, many authors pointed out the usefulness of FC in description of memory and hereditary properties of various materials and processes. The advantages of FD become apparent in mechanical and electrical properties modelling of real materials as well as in dynamical processes modelling of self-similar and porous structures. Fractional integrals and derivatives also appears in the theory of control and dynamic systems described by fractional differential equations [37]. Recently, the FC has been significantly examined in computer vision, particularly in image restoration, super-resolution, image segmentation and motion estimation [44]. Nowadays, it has been advantageously used in the modeling of various diseases such as the human immunodeficiency virus (HIV) [3] and malaria [36].

1.1.1 Fractional Order Derivatives

Several approaches of FD have been introduced over the ages. In this thesis, the choice has been reduced to those definitions which are related to the applications. Namely the Grünwald-Letnikov, Riemann-Liouville and Caputo's approximation. The first experiments and most of the presented research has been developed by the Grünwald-Letnikov since it is the basic one and most analyzed over time. In the last part of this thesis, all FD approaches mentioned above have been compared.

Before the definition of the FD, let's recall one of the basic functions of the FC, the Euler's gamma function $\Gamma(z)$.

$$\Gamma(z) = \int_0^\infty \mathrm{e}^{-t} t^{z-1} \, \mathrm{d}t, \tag{1.1}$$

The gamma function generalize the factorial $n!$ and allows n to take also non-integer and even complex values.

a) Grünwald-Letnikov

The FD definition by Grünwald-Letnikov is one of the first and basic approaches [21]. A direct definition of the $D^\alpha y(t)$ [37] is based on the finite differences of an equidistant grid in $[0, \tau]$, assuming that the function $y(t)$ satisfies certain smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{1.2}$$

with

$$\tau_{k+1} - \tau_k = h \tag{1.3}$$

and using the notation of finite differences

$$\frac{1}{h^\alpha} \Delta_h^\alpha y(t) = \frac{1}{h^\alpha} \left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^\alpha y(\tau_{n+1-v}) \right), \tag{1.4}$$

where

$$c_v^\alpha = (-1)^{v-1}\binom{\alpha}{v}, \tag{1.5}$$

the $D^\alpha y(t)$ by Grünwald–Letnikov from 1867 is defined as

$$^{\mathrm{GL}}\mathrm{D}^\alpha y(t) = \lim_{h\to 0} \frac{1}{h^\alpha} \Delta_h^\alpha y(t), \tag{1.6}$$

where $^{\mathrm{GL}}\mathrm{D}^\alpha y(t)$ denotes the Grünwald-Letnikov derivative of order α of the function $y(t)$, and h represents the sampling lattice.

b) Riemann–Liouville

Another classical form of the FD has been given by Riemann-Liouville. The left-inverse interpretation of $D^\alpha y(t)$ by Riemann-Liouville [37, 23] from 1869 is defined as

$$^{\mathrm{RL}}\mathrm{D}^\alpha y(t) = \frac{1}{\Gamma(n-\alpha)} \left(\frac{\mathrm{d}}{\mathrm{dt}}\right)^n \int_0^t (t-\tau)^{n-\alpha-1} y(t)\,\mathrm{dt}, \tag{1.7}$$

where $^{\mathrm{RL}}\mathrm{D}^\alpha y(t)$ denotes the Riemann–Liouville derivative of order α of the function $y(t)$, Γ is the gamma function and $n-1 < \alpha \le n, n \in \mathbb{N}, t > 0$.

c) Caputo

Nowadays, the most significant contributions to the field of FC are the results achieved by M. Caputo [7]. In contrast to the previous ones, the improvement lies in the unnecessity to define the initial FD condition [23, 37]. The Caputo's definition from 1967 is

$$^{\mathrm{C}}\mathrm{D}^\alpha y(t) = \frac{1}{\Gamma(n-\alpha)} \int_0^t (t-\tau)^{n-\alpha-1} y^n(t)\,\mathrm{dt}, \tag{1.8}$$

where $^{\mathrm{C}}\mathrm{D}^\alpha y(t)$ denotes the Caputo derivative of order α of the function $y(t)$, Γ is the gamma function and $n-1 < \alpha \le n, n \in \mathbb{N}, t > 0$.

1.2 Online Handwriting

The handwritten product from a person is conventionally acquired by a pen and paper. For the computerized analysis, the digitization of this pen-paper (offline) product must be performed (usually by a scanner). To overcome the limitations of this approach and to obtain a more robust and objective view of various hidden complexities of the handwriting process, new methods based on digitization and signal processing techniques have been developed [42, 40, 41, 39, 35, 4].

To acquire a variety of signals describing the evolution of handwriting in time the digitizing tablets (digitizers) have been used. Such a collection of handwritten data associated with timestamps is referred to as **online handwriting**. Online handwriting brings a possibility to quantify the kinematic components of the handwritten signal (velocity, acceleration and jerk) as well as the dynamic ones (pen pressure, tilt or azimuth). In addition, the in-air movement, i. e. movement of the pen tip up to 1.5 cm above the tablet's surface, is also acquired and can be analyzed. Such characteristics are very hard to be perceived and precisely quantified by a human observer and are almost impossible to be extracted using only the offline handwritten product.

1.2.1 Online Handwriting in people with handwriting difficulties

The inception of the handwriting abilities in school-aged children as well as the aging stages of handwriting in Parkinson's disease (PD) patients have been analysed in the scope of this dissertation.

a) Graphomotor disabilities in school aged children

Every school-aged child should be able to write legibly, in a well-coordinated way and fast enough. It is known that it takes approximately 10 years to develop handwriting skills [1] on both quantitative (speed) and qualitative (legibility) level [6, 43]. In general, until the age of 6, a child starts to develop graphomotor skills (GS) [2, 14] such as motor planning and execution, visual–perceptual abilities, orthographic coding, kinesthetic feedback, and visual–motor coordination, which eventually become automated at the age of 8–9 [20, 38]. The acquisition of GS is crucial for a child as it affects its academic success and further professional career [13]. Approximately 10–30 % of children experience graphomotor disabilities (GD) [14, 2] such as motor-memory dysfunction, graphomotor production deficits, motor feedback difficulties, etc. The impairment of the neuro-muscular system may cause serious pedagogical and psychological disabilities which can greatly affect a child's every-day life [16]. To provide children with preventive and therapeutic care, GD should be identified and treated as soon as possible. To identify and evaluate GD and associated handwriting difficulties (HD), occupational therapists and/or special educational counsellors use specialized questionnaires and tests. Nevertheless, their administration and coding are time-consuming, which limits their usage on a regular day-to-day basis. Furthermore, the lack of experience, perceptual capabilities and subjective judgement of an examiner together with complexity of GD/HD identification may lead to late and/or inaccurate diagnosis or even the children may remain undiagnosed.

b) Parkinson's disease dysgraphia

As population ages, the PD is expected to impose an increasing social and economic burden on societies [5]. It is the second most common neurodegenerative disorder with a prevalence rate estimated to approximately 2 % of the world population aged over 65 years [17]. Furthermore, the incidence rate is expected to be doubled within the next 12 years [18]. The most significant biological finding of PD is a rapid degeneration of dopaminergic cells in the substantia nigra pars compacta, even though the exact cause of PD has not yet been discovered. The primary motor symptoms of PD are tremor at rest, rigidity, bradykinesia and postural instability. Moreover, the cognitive impairment, sleep disturbances, depression and other non-motor symptoms may also arise. Furthermore, the additional axial motor symptoms may develop in PD patients such as dysphagia, hypokinetic dysarthria or gait freezing [19, 12, 8].

Considering the cognitive, perceptual and motor requirements of handwriting together with motor disturbances of PD patients, the disrupted handwriting may be used as a significant biomarker in PD diagnosis [9]. The progressive decrease of letter's amplitude or width, commonly known as micrographia, is the most observed handwriting abnormality in PD patients [24]. Moreover, the McLennan et al. [24] observed that in approximately 5 % of PD patients, micrographia may be observed even before the onset of the primary motor symptoms. On the other hand, some PD patients never develop micrographia, though, they still exhibit some other HD. Due to this complexity, the term PD dysgraphia has been established by Letanneux et al. [22]. The identification and proper description of PD dysgraphia in PD patients may lead to better understanding of the disease course. Furthermore, it can help to avoid the severe stages of the disease or even to suppress its symptoms, e. g. by the daily monitoring of the changes in handwriting in the treatment onset process.

1.3 Objectives

Concerning the superordinate analysis of this thesis (or entire doctoral study), the main objective of my dissertation is the **research of an advanced online handwriting parametrization utilized in the field of graphomotor disabilities analysis**, with a special focus on methods **based on fractional calculus**. More specifically, this dissertation aims to:

Aim 1: Propose a new online handwriting parametrization technique based on the fractional order derivatives. This constitutes conducting first experiments directly with fractional order derivatives and their potential in HD analysis by on-line handwriting. The FD will substitute the conventionally used differential derivatives in the kinematic handwriting features extraction.

Aim 2: Investigate the discrimination power and descriptive abilities of the new FD-based features in PD dysgraphia analysis. Specifically, investigate the relationship between the newly designed FD-based features and the patient's clinical data. Next, evaluate the discrimination power of the FD-based features in terms of the sensitivity and specificity. Subsequently, establish regression models using the FD-based features that will estimate the severity of PD. And finally, identify handwriting or a drawing task/tasks that provide the best results in terms of PD dysgraphia analysis. All results and performance abilities will be compared to the baseline. Furthermore, the experiment on a multilingual cohort of PD patients will be performed.

Aim 3: Investigate the discrimination power and descriptive abilities of the new FD-based features in GD analysis in school-aged children. The aim 3 is similar to the previous aim number 2, but instead of PD dysgraphia, the GD in school-aged children will be the point of interest, excluding the multilingual cohort analysis.

Aim 4: Optimize the computational performance of the new features. Over the entire development of the new parametrization technique, the optimization of the FD and its computational performance has to be done. The optimal range of the α order will be investigated to reduce the computational cost of the analysis.

Aim 5: Explore the differences and compare the performance of several FD approaches in GD assessment. To bring a more general view of the research, several FD-approaches will be compared in GD analysis. To evaluate the power of the features to assess the GD, the multivariate regression analysis will be performed.

2 Summary of the Publications

The main part of this dissertation is based on the eighth selected papers published during my doctoral studies. This section gives a brief summary of these publications, their contextual connections, and it explains how the previous work and research visits affected the research direction and the topic of this thesis. For better understanding, the timeline of all key events is presented in Table 2.1. The Publications are presented in versions of accepted or submitted manuscripts. Their templates are unified, however the contents is unmodified, apart from the tables, figures and equations numbering.

Prior to the research focused on FD possibilities in GD, I was working on the acoustic analysis of disrupted speech/voice for the identification of hypokinetic dysarthria in PD patients. Achievements in this research field have been published in three conference papers (winning paper at EEICT 2017) [25, 27, 28] and one journal article [29] by me as the first author. Furthermore, several publications have been published where I am a co-author.

In April 2018, I participated in a one month research visit to the Pompeu Fabra University, TecnoCampus Mataró, Barcelona, where Prof. Marcos Faundéz-Zanuy proposed a new direction of my research towards the exploration of the FC possibilities in the online handwritten signal produced by PD patients. This resulted in a preliminary study entitled Fractional Derivatives of Online Handwriting: A New Approach of Parkinsonic Dysgraphia Analysis [34]. To the best of our knowledge, this study was the first of its kind, which employed the FD in kinematic analysis of online handwriting. This study revealed the impact of FD-based features in the analysis of PD dysgraphia. In comparison with results reported in other works, the newly designed features increased the classification accuracy by 8 % in univariate analysis and by 10 % when employing the multivariate one.

At the beginning of the year 2018, I have been awarded a grant for the mobility of researchers, starting in June 2018. Due to the previous collaboration with Prof. Marcos Faundéz-Zanuy, I was given the opportunity to continue my research as a part of his team in TecnoCampus Mataró. Soon, Prof. Marcos Faundéz-Zanuy became the official supervisor specialist of my dissertation. This cooperation led to significant publications starting with the conference paper entitled Advanced Parkinson's Disease Dysgraphia Analysis Based on Fractional Derivatives of Online Handwriting [30]. This study followed the preliminary exploration of the FD possibilities in the quantitative PD dysgraphia analysis. The study confirmed that FD brings a new promising and enhancing methodology of PD diagnosis. Based on the results, we were able to identify PD dysgraphia with almost 90 % accuracy using only 5 basic kinematic features extracted from a few handwriting tasks. This work was chosen to be extended for a special issue in the journal *Applied Sciences (IF 2.217, Q3)*.

Table 2.1: Timeline

2016–2017 Prior work
First published experiments with acoustic analysis of poem recitation for identification of hypokinetic dysarthria in PD patients.

04–05/2018 Pompeu Fabra University, TecnoCampus Mataró, Barcelona, Spain
Short term research stay, exchanged ideas, new research direction proposed by Prof. Marcos Faundez-Zanuy.

06/2018 Fractional Derivatives of Online Handwriting
Pilot study on FD impact in kinematic analysis of PD dysgraphia.

06/2018–06/2019 Pompeu Fabra University, TecnoCampus Mataró, Barcelona, Spain
Collaboration with and supervision by Prof. Marcos Faundez-Zanuy in advanced signal processing, mathematical modelling, and statistical analysis. Strong focus on the research and application of FD in HD analysis.

10/2018 Advanced Parkinson's Disease Dysgraphia Analysis
An extended study of FD possibilities and their enhancement in PD dysgraphia identification.

10/2018 Istanbul Gelisim University, Turkey
The training school on *Advantages of the fractional models in dealing with real world problems* lead by Prof. Dumitru Baleanu.

12/2018 Identification and Monitoring of Parkinson's Disease Dysgraphia
A complex investigation of the FD possibilities in PD dysgraphia diagnosis and monitoring based on online handwriting/drawing parameterization. The study proposed new advances in kinematic analysis based on FD.

- **03/2019 Analysis of Online Handwriting in a Multilingual Cohort**
  A unique study, dealing with PD dysgraphia analysis using FD in online handwriting in multilingual cohort (Czech and Spanish).

- **09/2019 Optimization of Fractional Order Derivatives**
  Optimization of the computational performance and identification of the optimal α order values. For the first time, the kinematic analyses have been extended by analysis of handwriting dynamics.

- **10/2019 Fractional Order Derivatives in Assessment of Handwriting Difficulties in Children**
  The first study investigating the possibilities of FD in the computerized assessment of HD in school-aged children.

- **07/2020 Advanced Parametrization of Graphomotor Difficulties in School-aged Children**
  A study presenting three novel types of graphomotor features (modulation spectra, FD, and tunable Q-factor wavelet transform), providing more robust and complex quantification of GD in school-aged children.

- **11/2020 Analysis of Various Fractional Order Derivatives Approaches**
  A unique and exploratory study that will perform an investigation of the various FD approaches in the computerized assessment of GD in school-aged children. (submitted)

- **Future work**
  Extend the analysis of several FD approaches. Investigate the mathematical modelling of HD using advanced FC methods.

Legend: – Journal article, – Conference paper, – Research visit

In October 2018, I attended an eminent training school on *Advantages of the fractional models in dealing with real world problems* led by Prof. Dumitru Baleanu at the Istanbul Gelisim University in Turkey. World-class researchers in the field of FC generously shared their knowledge during the training school. This new information has been interest-bearing during the preparation of the journal article entitled Identification and monitoring of Parkinson's disease dysgraphia based on fractional-order derivatives of online handwriting [31] published in *Applied Sciences (IF 2.217, Q3)*. This work extended the previously mentioned conference paper, where the impact of FD on the PD dysgraphia diagnosis and monitoring was explored more deeply. It investigates the relationship between newly designed FD handwriting features and the patient's clinical data. Moreover, it evaluates the discrimination power of the FD features and uses the XGBoost regression models to estimate the severity of PD. All results were compared to the baseline and they suggest an improvement of the computerized PD severity assessment.

A collaboration with the Neurology Unit of the Mataró Hospital led to the conference paper Advanced Analysis of Online Handwriting in a Multilingual Cohort of Patients with Parkinson's Disease [33]. Mataró Hospital disposes of a database of PD patient's handwritten products, similar to our Czech PaHaW database [10]. Therefore, we created a study, analyzing a multilingual cohort involving those two PD handwriting databases (Czech and Spanish) in order to train a more robust classification model. To the best of our knowledge, this is the first study considering a multilingual cohort in PD dysgraphia analysis. In this work, the high discrimination power of the FD-based parameters has been observed and the high impact of online handwriting processing in cross-cultural PD dysgraphia analysis studies has been proven.

In order to extend the previous findings and perform a deeper and more sensitive analysis of FD-based features, especially in terms of their discrimination power and descriptive abilities, the conference paper Analysis of Parkinson's Disease Dysgraphia Based on Optimized Fractional Order Derivative Features [26] was created and presented at the prestigious European Signal Processing Conference 2019. For the first time, the FD-based features have been extracted also from other dimensions of online handwriting, like pressure, azimuth, and tilt. Moreover, we identified the optimal values of the α order for FD employment in the field of PD dysgraphia analysis. Identification of these ranges enables a significant reduction of computational costs (by approximately 50 %) because researchers do not have to explore the full range of possible values of the FD order during the quantitative analysis of PD dysgraphia.

After the success of the FD-based features in the field of the PD dysgraphia analysis, the investigations of the FD impact in the quantitative assessment of GD in school-aged children has been executed. The pilot study, entitled Fractional Order Derivatives Evaluation in Computerized Assessment of Handwriting Difficulties in School-aged Children [45], indicates that FD-based features bring benefits of a more robust quantification of in-air movements as opposed to the conventionally used one.

Based on the indications from previous works, the complex study investigating the improvements of the quantitative assessment of GD has been published in *IEEE*

Access (IF 3.745, Q1), entitled Advanced Parametrization of Graphomotor Difficulties in School-aged Children [15]. In this study, three novel advanced handwriting parametrization techniques based on FD, modulation spectra and tunable Q-factor wavelet transform have been proposed to improve the identification of GD using online handwriting. My contribution to this study is naturally FD-related. The results showed that combining the proposed graphomotor features with the set of conventionally used ones can increase the prediction capability of the trained binary classifier significantly, and thanks to that help with the early diagnosis of HD frequently manifested in developmental dysgraphia.

Throughout the previous research, only one approach of the FD has been used, namely the Grünwald-Letnikov approximation. Therefore, as the next natural step, the examination of the various FD approaches has been performed. Riemann–Liouville's and Caputo's approaches together with the Grünwald-Letnikov's have been investigated in the computerized assessment of GD in school-aged children. The examination showed that employment of various FD approximations brings major differences in kinematic handwriting features. In the scope of the correlation analysis associated with the overall score, the Caputo's FD approach exceeds the rest of the analysed FD approximations. However, in the scope of the sub-score, the Riemann-Liouville gained the most significant features. Moreover, the results of the multivariate analysis suggest that the Riemann-Liouville's approximation in the field of quantitative GD analysis outperforms the other ones. These findings have been submitted to the IEEE Access (IF 3.745, Q1), entitled Analysis of Various Fractional Order Derivative Approaches in Assessment of Graphomotor Difficulties [32]. At the time of writing this thesis, the article is in the second round of the review.

3 Concluding Discussion

To conclude the dissertation, this section sums up the conclusions of the publications and is structured in such a way that it addresses the objectives in order of appearance in the section Objectives.

In the scope of the **Aim 1**, a new online handwriting parametrization technique based on the fractional order derivatives had to be proposed. In the pilot study [34], a new methodology of the feature extraction has been introduced, utilizing the Grünwald-Letnikov FD approach. This newly proposed method of the kinematic features extraction substitutes the conventionally used differential derivatives, and with the possibility of an arbitrary order α brings an infinite variation of the basic kinematic features. According to the results reported in Table I.2, the hypothesis, that the application of the FD in the calculation of the kinematic features will bring promising and enhancing methodology in the automatic diagnosis of the PD dysgraphia has been confirmed. These observations were further examined and confirmed also in paper [30]. Regarding the reported values of the order α (all non-integer) of the kinematic features included in the finest models of the classification analysis (univariate and multivariate, see Table II.3), it is evident that features extracted by FD fully surpassed the conventional ones. Considering the above-mentioned achievements, the fulfillment of the **Aim 1** can be concluded.

From the beginning of the research, the proposed parametrization technique has been monitored and evaluated by its discrimination power since it is the most common criterion of disorder analysis performance. Regarding our parallel research in PD analysis, the discrimination power was investigated on handwritten data acquired from PD patients. In the pilot study [34], the results of the discrimination analysis (see Table I.2) showed promising improvements. The classification accuracy based on features extracted from the Archimedean spiral task was up to 10 % higher in comparison with the baseline. Results from the pilot study have been confirmed by the following study [30], where the best classification model reached 89.81 % accuracy, 88.63 % sensitivity, and 90.87 % specificity (see Table II.3) using features from various handwritten tasks. In comparison with the baseline [11], the accuracy is almost the same (89 %), nevertheless, the baseline model includes a combination of kinematic and pressure features, whereas the proposed new approach is using only basic kinematic ones. In the following study [31], the machine learning pipelines used for analysis were improved by using the state-of-the-art XGBoost algorithm. This improvement surprisingly resulted in a very high classification performance of 97.74 % accuracy, 95.50 % sensitivity, and 100 % specificity (see Table III.6), though achieved by a baseline feature (median of the horizontal velocity of a sentence). The FD-based proposed approach resulted in 87.14 % accuracy, which is approx. 10 %

lower in comparison with the conventionally used features. Contrary to our pilot results, newly proposed features did not lead to any improvements in this case. After a deeper analysis, it was found that this was caused by a combined task approach and that the FD-based features work better in specific continuous and/or repetitive tasks, such as the Archimedean spiral (for more details please read Section III.4). This was also confirmed in the following study [26] (see Table V.2 and Table V.3) published at EUSIPCO 2019, which is focused on the optimization of FD-based handwritten features. Considering all those findings, the part of the **Aim 2** focusing on the investigation of the discrimination power of the new FD-based features in PD dysgraphia analysis has been fulfilled.

In addition to the investigation of the discrimination power of the newly designed features, the exploration of their descriptive abilities has been performed too as a part of the **Aim 2**. Based on the results published in [31], the FD-based features correlate more significantly with the clinical characteristics of PD (see Table III.5). Especially, the strong correlation has been observed for handwriting tasks based on the periodic repetition of specific movements. Regarding the results achieved by the regression analysis, the FD-based features are more suitable for modelling of PD severity. For instance, in [31] the newly proposed features outperformed the conventional ones in the estimation of the UPDRS V score (EER = 12.51 %). These results have been also confirmed in the following study [26], where the regression has been performed on separate tasks in addition to the previous one (see Table V.2 and Table V.3).

Another sub-objective was to identify the best handwriting task/tasks for the quantitative PD dysgraphia analysis. In [30] we identified the repetitive loops and sentence tasks as the most significant ones based on the result of the univariate classification analysis (see Table II.3). In [31] these handwriting tasks again emerged with the best results of the analysis, nevertheless, the repetitive letter l and the Archimedean spiral achieved similarly good results. Furthermore, based on the results of the optimization study [26], these tasks again aroused as the best ones (see Table V.3). Considering this, the most suitable handwriting tasks for the analysis of PD dysgraphia using the FD-based features are repetitive based. Besides that, the experiment on the multilingual cohort (Czech and Spanish) of PD patients involving the newly proposed approach has been performed [33]. Using all knowledge obtained by the previous research, more than 80 % classification accuracy in all scenarios was achieved (see Table IV.2). Therefore, the high impact of online handwriting processing in cross-cultural PD dysgraphia analysis has been proven. Regarding all the above-mentioned knowledge and results, the **Aim 2** can be considered fulfilled.

In addition to the PD analysis, our team started another parallel research focused on GD analysis in school-aged children. Therefore, the next natural step of the FD-based handwriting features development was to investigate its discrimination power and descriptive abilities on the handwritten data acquired from this research (**Aim 3**). The results published in [45] showed, that a single feature will not have sufficient discrimination power (see Figure VI.3) to differentiate between a child with and without GD. Moreover, based on the results of the Mann-Whitney U-test, the selected task in this particular study (an alphabet) is not very suitable for this kind of analysis. As the most significant handwriting features emerged the newly proposed FD-based features (derived from the acceleration of in-air movement). In our comparative study [15], where three novel graphomotor features have been introduced and compared (FD-based, modulation spectra, and tunable Q-factor wavelet transform), the FD-based features achieved the highest classification accuracy (75 %, see Table VII.3). The conventionally used features showed a similar result (73 %), however, when these features are combined, the classification performance can be increased by approximately 10 %.

The results reported in [45] indicated a statistically significant relationship between the HPSQ-C and FD-based features extracted from the in-air movement (see Table VI.2). These movements are likely to describe inter-stroke hesitation/s, uncertainty during writing, stiffness of hand/fingers, etc., which can be linked with GD and are imperceptible to an examiner that only sees the written product. From the results reported in [15], it can be observed that the top-ranking non-conventional features (FD-based included) mostly consisted of basic kinematic and dynamic features as opposed to the baseline, which consisted solely of the spatial and dynamic ones (see Table VII.2). Moreover, all of the FD-based most significant features have been extracted from different graphomotor tasks further underlying the need for a variety of specifically designed features to quantify GD.

Based on the results of the regression analysis performed in [32], where the score of the GD severity has been estimated, the FD-based features resulted in the mean absolute error 0.65 (see Table VIII.6). If we take into account that the range of the scale is 4, the error can be considered as very low. In fact, when assessing GD in children, psychologists tend to make the error even higher, e. g. two experts can frequently differ by 1 point (compare it to 0.65). Regarding the sub-objective oriented to the identification of the most suitable handwriting task/tasks for GD analysis in school-age children, based on the results reported in [45], the alphabet task can be considered as not suitable for this analysis. The observations presented in [15] suggest, that the tasks based on the repetition of the simple movement (spirals, connected loops, and sawtooth) are the most suitable for the quantification of the GD in school-aged children. It is important to stress out, that the nature of the best handwriting tasks for GD analysis in school-aged children is the same as for the analysis of PD dysgraphia. Considering all the findings mentioned in the above three paragraphs, it can be concluded that the **Aim 3** has been fulfilled.

Even though the optimization of the FD-based features has been done continuously from the beginning of the research, the study published at EUSIPCO 2019 [26] has been specifically focused on the optimization of the α order. The repetitive loops and sentence handwriting tasks from the PaHaW database [10] have been selected for this investigation. FD-based handwriting features have been extracted in the α range from 0.01 to 1.00 with 0.01 step (100 FD-based features for one time sequence) to identify the optimal values of α. Based on the results presented in Figure V.2, the optimal α for PD classification is in the ranges from 0.05 to 0.35 and from 0.60 to 0.75. Next, the optimal value of α for PD severity assessment and duration estimation is in the ranges from 0.05 to 0.45 and from 0.65 to 0.80. By intersecting the optimal α ranges of the classification and regression analysis, the final optimal ranges of α from 0.05 to 0.45 and from 0.60 to 0.80 have been established, which is recommended to be used in the field of PD dysgraphia analysis. In addition to the α range optimization, the algorithm for FD calculation has been improved by segmentation-based computation (up to 80 % less run-time). Considering all the mentioned achievements, the **Aim 4** has been satisfied. Nevertheless, an optimization of α order for GD analysis in school-aged children is missing and has to be executed in future research.

To extend the previous research, the comparative study of various FD-approaches has been performed [32]. In addition to the Grünwald-Letnikov's approach, the Riemann-Liouville's and Caputo's FD approaches have been explored. A comparison of an identical feature (i. e. velocity for $\alpha = 0.2$, see Figure VIII.8) confirms the hypothesis of different feature behaviour across the FD approaches. Similarly, the comparison in Figure VIII.10, where the dependency of the relative standard deviation of velocity on the FD order α is visualized. Regarding the results of correlation analysis, the most significant features are extracted by the Caputo's FD (see Table VIII.4 and VIII.5). Concerning the multivariate analysis (see Table VIII.6), where the GD severity has been estimated, the best results (MAE = 0.65) were achieved by the Riemann-Liouville FD-based features. Based on these findings, it can be concluded that the employment of various FD approximations brings major differences in kinematic handwriting features. It needs to be pointed out, that this comparison has been performed by employing one handwriting task only (combined loop task from school-aged children dataset). Therefore, more handwriting tasks should be included in the analysis and investigation should be done on the PD database as well. Nevertheless, regarding the observation mentioned in the above paragraph, the fulfillment of the **Aim 5** can be concluded.

Beyond State of the Art. This section that briefly lists the achievements in fact summarizes four long years of hard work:

- new advanced parametrization methodology based on fractional order derivatives has been introduced
- proposed methodology outperforms the conventionally used ones in several disciplines of PD dysgraphia analysis
- proposed methodology improves current state-of-the-art techniques of GD analysis in school-aged children
- proposed methodology has been optimized in the scope of the computational performance as well as in FD order fine-tuning
- various FD-approaches have been compared to identify the most suitable ones for particular areas of GD analysis

Future directions. Regarding the conclusions presented in the section above, the introduced research can be considered as a pilot in nature, even though the results proved the improvements in GD analysis. As the next step, the optimization of the alpha order has to be performed in the scope of GD in school-aged children. The FD optimization has to be executed separately for each handwritten task used for the GD analysis to obtain the fine-tuned task-dependent handwritten features. Moreover, various FD approaches have to be analyzed more deeply (also in the scope of both steps mentioned above) to identify the most suitable variation or combination for GD analysis. Subsequently, the research will be further extended by the analysis of a multilingual cohort dataset. This part of the research will be crucial to generalize the proposed methodology. Furthermore, the focus will be concentrated on other advanced techniques, starting with modelling of the neuromotor processes during handwriting by Sigma-Lognormal models.

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Publications

I Fractional Derivatives of Online Handwriting: a New Approach of Parkinsonic Dysgraphia Analysis

Outline

Bibliographic Information

J. Mucha, V. Zvoncak, Z. Galaz, M. Faundez-Zanuy, J. Mekyska, T. Kiska, Z. Smekal, L. Brabenec, I. Rektorova and K. Lopez-de-Ipina. Fractional Derivatives of Online Handwriting: A New Approach of Parkinsonic Dysgraphia Analysis. In *2018 41st International Conference on Telecommunications and Signal Processing (TSP)*, pages 1-4. IEEE, 2018. `doi:10.1109/TSP.2018.8441293`.

Author's Contribution

The author surveyed related works, co-proposed a new method, designed and performed the analysis, and wrote a significant part of the manuscript. He was also working on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder. One typical hallmark of PD is disruption in execution of practised skills such as handwriting. This paper introduces a new methodology of kinematic features calculation based on fractional derivatives applied on PD handwriting. Discrimination power of basic kinematic features (velocity, acceleration, jerk) was evaluated by classification analysis (using support vector machines and random forests). For this purpose, 30 PD patients and 36 healthy controls were enrolled. In comparison with results reported in other works, the newly designed features based on fractional derivatives increased classification accuracy by 8 % in univariate analysis and by 10 % when employing the multivariate one. This study reveals an impact of fractional derivatives based features in analysis of Parkinsonic dysgraphia.

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I.1 Introduction

Parkinson's disease (PD) is the second most frequent progressive neurodegenerative disorder in the world [5]. Its prevalence rate is estimated to approximately 1.5 % for people aged over 65 years [26]. Although, the exact pathophysiological cause of PD has not yet been discovered, a rapid degeneration of dopaminergic cells in *substancia nigra pars compacta* [14] emerged as the most significant biological finding associated with the disease. Tremor in rest, rigidity, bradykinesia, and loss of postural reflexes [20, 8] are considered as cardinal motor symptoms. PD also accompanies several non-motor symptoms such as sleep disorders, cognitive deficits, depression, dementia, etc. [1, 21].

Due to motor dysfunctions in people suffering from PD, some recent studies have suggested that quantitative analysis of handwriting can be used as a quick and accurate PD diagnosis method [25, 6]. Moreover, using digitizing tablets we are able to acquire online handwriting signals, where a temporal information is added to x and y coordinates. Therefore the analysis is not limited to spatial features quantifying mainly PD micrographia, but in addition, we are able to quantify temporal, kinematic and dynamic manifestations of PD (e. g. hesitations, pauses, and slow movement [4]), which are generally called PD dysgraphia [16].

For the purpose of PD handwriting analysis, several handwriting tasks were proposed (Archimedean spiral, repetitive loops, letters, words, sentences, etc.), but the most popular handwriting task for tremor assessment is currently the Archimedean spiral [8]. This task has been frequently used to evaluate motor performance in various movement disorders [10, 28], including PD. In view of these facts the Archimedean spiral was selected for the purposes of this study as well. Some related works (2014–now) focused on analysis of online handwriting in PD patients are summarized in Table I.1.

The aim of this paper is to introduce advanced kinematic features that replace the conventional ones by utilizing fractional derivative (FDE). The potential of FDE in PD dysgraphia quantification is demonstrated by classification analysis and a discrimination power of the newly designed features is compared with a baseline [8, 10, 6, 7].

I.2 Materials and Methods

I.2.1 Dataset

The dataset consisted of 66 participants: 36 healthy controls (HC) with (mean $\pm$ std) age: 62.50 $\pm$ 11.70 years, and 30 PD patients with (mean $\pm$ std) age: 68.37 $\pm$ 11.08

Table I.1: Overview of related works focused on analysis of PD dysgraphia

First author	**Year**	**PD/HC**	**Handwriting task**	**Analysis**	**Features**	**Conclusions**
Broeder [3]	2014	18/11	Repetitive loops	Correlation (Spearman)	Writing amplitude and velocity	The highest correlation for given medical scale and task was with velocity with $r = 0.627$.
Drotar [7]	2014	37/38	One sentence	Differential analysis (SVM)	Kinematic, temporal, spatial and its statistical representations	Using both in-air/on-surface features resulted in 85.61 % classification accuracy.
Drotar [9]	2015	37/38	Characters, words, sentences	Differential analysis (SVM)	Same as in [7], entropy, empirical mode decomposition, signal energy	The highest classification accuracy after feature selection approach was 88.1 %.
Drotar [10]	2015	37/38	Characters, words, sentences	Differential analysis (SVM)	Same as in [9], pressure	Classification performance was at its peak with on-surface features (89.09 %).
Drotar [8]	2016	37/38	Characters, words, Archimedean spiral, sentences	Differential an. (SVM, K-NN, AdaBoost)	Same as in [10], but in-air features were not computed	For classification of PD on all exercises SVM proved to be the best classifier with accuracy 82.5 %.
Heremans [13]	2015	34/10	Up/down strokes at varying amplitudes	ANOVA	Writing amplitude and velocity	Significant difference between groups was in writing amplitude ($F(2.41) = 3.97; p = 0.03$).
Heremans [12]	2016	30/15	Repetitive cursive loops	ANOVA, correlation	Writing amplitude and velocity	Medical scale and writing amplitude had significant correlation $r = -0.40$.
Loconsole [17]	2017	4/7	Sentence, repetitive loops	Differential analysis (ANN)	Execution time and average speed, density ratio, height ratio	Highest classification accuracy 96.81 % was achieved using all the extracted features.
Masarova [18]	2014	40/40	Characters, words, Archimedean spiral, sentences	Correlation (Spearman)	Velocity, acceleration, jerk, statistical representations of each one	The most significant relative difference between groups was 19.5 % for mean velocity of writing extracted from long sentence.
Nackaerts [22]	2017	38/0	Repetitive loops, eight-like figure	Correlation (Spearman)	Stroke duration, writing velocity, normalized jerk	Amplitude training has as negative effect on fluency and stroke duration.
Smits [28]	2014	10/10	Circle, spiral, line characters, sentence	t-test	Kinematic, temporal, spatial and its statistical representations	Time per repetition, velocity, and acceleration have the highest discriminative power.

SVM – support vector machine; r_s – Spearman's correlation coefficient; K-NN – K-nearest neighbours; ANOVA – analysis of variance; ANN – artificial neural network; F and p corresponds to variables of F distribution; articles are sorted alphabetically and then by year of release.

years, PD duration: 8.67 ± 4.49 years, UPDRS V (Unified Parkinson's disease rating scale, part V: Modified Hoehn & Yahr staging score) [11]: 2.23 ± 0.83 and LED (L-dopa equivalent daily dose) [15]: 1474.67 ± 614.81 mg. The participants were enrolled at the First Department of Neurology, St. Anne's University Hospital in Brno, Czech Republic. All participants reported Czech language as their native language and all participants were right-handed. The PD patients completed the tasks approximately 1 hour after their regular L-dopa medication. All participants signed an informed consent form approved by the local ethics committee.

I.2.2 Data Acquisition

The Archimedean spiral task is a part of the PaHaW database [8]. During this task, a template was shown to a subject for visual guidance. Participants drew the spiral from its center, but were not asked to draw it within particular boundaries or to follow a pre-drawn line. Online handwriting signals were recorded using the Intuos 4M (Wacom technology) digitizing tablet, with sampling rate $f_s = 100$ Hz. The tablet was overlaid with an empty paper template. The following features were acquired (time sequences): x and y coordinates – $x[t]$, $y[t]$; time-stamp – t; in-air/on-surface status – $b[t]$; pressure – $p[t]$; azimuth $az[t]$; and tilt $al[t]$.

I.2.3 Fractional Derivative

Several approaches of fractional derivative calculation exist [23]. In this paper, the implementation of FDE by Jonathan Hadida, which follows the Grünwald-Letnikov approximation [27], was used. A direct definition of the FDE $D^\alpha y(t)$ is based on finite differences of an equidistant grid in $[0, \tau]$. Assume that the function $y(\tau)$ satisfies some smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{I.1}$$

with

$$\tau_{k+1} - \tau_k = h \tag{I.2}$$

and using the notation of the finite differences

$$\frac{1}{h^\alpha}\Delta_h^\alpha y(t) = \frac{1}{h^\alpha}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^\alpha y(\tau_{n+1-v})\right), \tag{I.3}$$

where

$$c_v^\alpha = (-1)^{v-1}\tbinom{\alpha}{v}, \tag{I.4}$$

the Grünwald-Letnikov implementation is defined as [23]:

$$D^\alpha y(t) = \lim_{h \to 0} \frac{1}{h^\alpha}\Delta_h^\alpha y(t), \tag{I.5}$$

where $D^{\alpha}y(t)$ means a derivative with order α of function $y(t)$, and h represents sampling lattice.

In our case, the FDE substitutes the conventional differential derivative during calculation of the kinematic features. A detailed description of the FDE can be found at [23, 27].

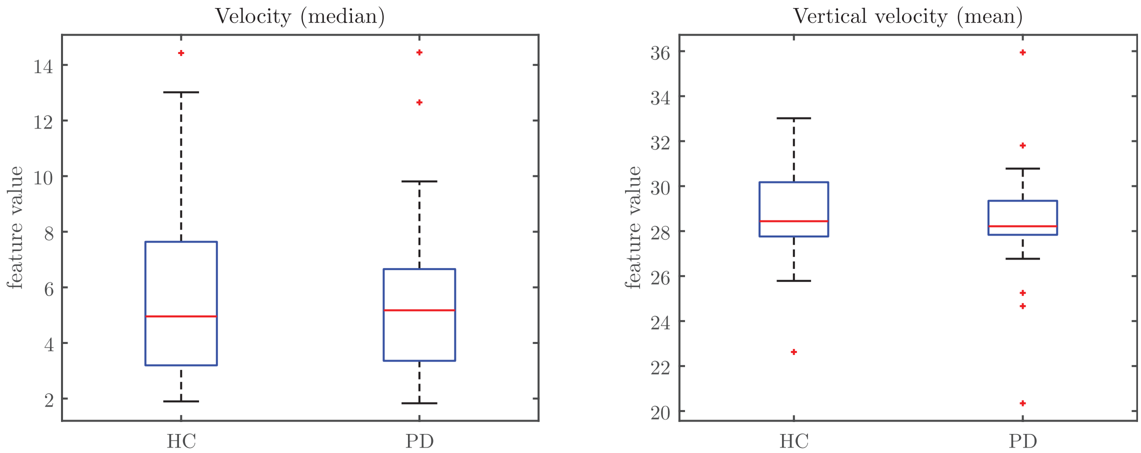

Fig. I.1: Box plots of two features with the highest MCC (univariate models).

I.2.4 Handwriting Features

To demonstrate the impact of FDE in analysis of PD dysgraphia, we extracted only basic on-surface kinematic parameters [8, 6]: velocity – rate at which a position of pen changes with time [mm/s]; acceleration – rate at which the velocity of pen changes with time [mm/s^2]; jerk – rate at which the acceleration of pen changes with time [mm/s^3]; and their horizontal and vertical variants. These features were calculated for different orders α of the FDE in range from 0.1 to 1.0 with 0.1 steps. Consequently, statistical properties of the features were described using following statistics: mean, median, standard deviation (std), and maximum (max) [8, 10, 6, 7]. In total 360 features were extracted.

I.2.5 Statistical Analysis

To evaluate a discrimination power of the features, univariate binary classification (PD/HC) models (stratified 7-fold cross-validation with 50 repetitions) based on random forests (RF) [2] and support vector machines (SVM) [29] with radial basis function (RBF) were employed. Next, some improvements in classification accuracy were done by multivariate approach with the same classifiers and the same cross-validation settings. In this case, the sequential floating forward selection (SFFS) algorithm was used [24] in order to select the most appropriate combination of the features. Classification performance was evaluated by the Matthew's correlation coefficient [19], classification accuracy (ACC), sensitivity (SEN) and specificity (SPE).

I.3 Results

Results of the univariate and multivariate analysis are summarized in Table I.2. Regarding the univariate classification, only the best features (in terms of the MCC values) are reported. The best feature of the univariate classification is median of velocity with $\alpha = 0.1$ (ACC = 70.55 % classified by SVM). Box plots of two features with the highest MCC are visualized in Figure I.1. Regarding the multivariate classification analysis, ACC of 72.39 % (MCC = 0.44) was achieved using combination of 10 features classified by RF. The set of these features as gradually selected by SFFS can be found in Table I.3.

Table I.2: Results of the univariate and multivariate classification analysis

Univariate analysis						
Classifier	Feature	α	MCC	ACC [%]	SEN [%]	SPE [%]
SVM	velocity (median)	0.1	0.40	70.55	62.00	77.67
SVM	vertical velocity (mean)	0.6	0.40	70.24	52.40	85.11
RF	jerk (max)	1.0	0.33	67.06	59.53	73.34
RF	vertical jerk (median)	0.1	0.29	65.34	54.40	74.45
Multivariate analysis						
Classifier	Number of features		MCC	ACC [%]	SEN [%]	SPE [%]
RF	10		0.44	72.39	65.52	77.87
SVM	11		0.39	67.55	57.42	79.96

α – order of fractional derivative; RF – random forests; SVM – support vector machine; MCC – Matthew's correlation coefficient; ACC – accuracy; SEN – sensitivity; SPE – specificity.

I.4 Discussion

According to the reported results we can confirm our previous hypothesis that application of the FDE in calculation of kinematic features brings promising potential in automatic diagnosis of PD dysgraphia. Considering that only the basic kinematic features such as velocity, acceleration, and jerk were extracted, the results of discrimination analysis are promising, especially when compared with previous related papers (baseline) [8, 10, 6, 7], where the Archimedean spiral task was eliminated from the final classification models due to low ACC (62–65 %). In the case of univariate analysis we can claim that the ACC was improved by 3–8 %. Based

Table I.3: The best combination of features in the multivariate classification (employing RF) selected by SFFS

Feature	α	ACC [%]
vertical jerk (median)	0.1	64.89
acceleration (mean)	0.3	65.97
horzintal velocity (median)	0.1	68.17
vertical jerk (mean)	0.8	70.34
horzintal velocity (median)	0.4	71.52
vertical acceleration (median)	0.5	71.15
horzintal acceleration (median)	1.0	72.36
vertical acceleration (median)	0.6	71.77
velocity (median)	0.8	72.01
horzintal jerk (median)	1.0	72.39

on the results summarized in Figure I.1, we can confirm reduced movement abilities in PD cohort, which is caused mainly by rigidity and bradykinesia. The best result of multivariate analysis (ACC $=$ 72.38 %, MCC = 0.44) was achieved by the RF classifier in combination with 10 features selected by SFFS. In comparison to the baseline, this result means improvement by 10 %. Moreover, from the feature set description (see Table I.3), it is evident that most of the parameters were based on $\alpha \neq 1$, which confirms full utilization of the FDE.

I.5 Conclusion

With respect to the results we can conclude that using the FDE in kinematic analysis brings new improvements in quantitative PD dysgraphia processing and add-on to the existing conventional techniques. This study is considered as a pilot one and its conclusions should be confirmed and extended by further research. For instance, it would be interesting to combine the newly developed parameters with other features such as temporal, spatial or dynamic ones. Moreover, the other tasks (e.g. overlapped circles, words, drawings) could be quantified. Another implementation of the FDE should be evaluated as well. Finally, a bigger dataset must be used to be able to generalize the conclusions.

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II Advanced Parkinson's Disease Dysgraphia Analysis Based on Fractional Derivatives of Online Handwriting

Outline

Bibliographic Information

J. Mucha, J. Mekyska, M. Faundez-Zanuy, K. Lopez-de-Ipina, V. Zvoncak, Z. Galaz, T. Kiska, Z. Smekal, L. Brabenec and I. Rektorova. Advanced Parkinson's Disease Dysgraphia Analysis Based on Fractional Derivatives of Online Handwriting. In *2018 10th International Congress on Ultra Modern Telecommunications and Control Systems and Workshops (ICUMT)*, pages 1-6. IEEE, 2018. `doi:10.1109/ICUMT.2018.8631265`.

Author's Contribution

The author surveyed related works, co-proposed a new method, designed and performed the analysis, and wrote a significant part of the manuscript. He was also working on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

Parkinson's disease (PD) is one of the most frequent neurodegenerative disorder with progressive decline in several motor and non-motor skills. Due to time-consuming and partially subjective conventional PD diagnosis, several more effective approaches based on signal processing and machine learning, e. g. online handwriting analysis, have been proposed. This paper introduces a new methodology of PD dysgraphia analysis based on fractional derivatives applied in PD handwriting quantification. The proposed methodology was evaluated on a database that consists 33 PD patients and 36 healthy controls who performed several handwriting tasks. Employing random forests classifier in combination with 5 kinematic features based on fractional-order derivatives we reached 90 % classification accuracy, 89 % sensitivity, and 91 % specificity. In comparison with the results of other related works dealing with the same database, the proposed approach brings improvements in PD dysgraphia diagnosis and confirms the impact of fractional derivatives in kinematic analysis.

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II.1 Introduction

Parkinson's disease (PD) affects millions of people all over the world as a second most frequent neurodegenerative disorder [4]. Prevalence rate of PD is estimated to approximately 1.5 % for people aged over 65 years [31], but the risk of being affected by this disease increases strongly with age [5]. The cardinal signs of PD include resting tremor, slowness of movement (bradykinesia), rigidity and postural instability [10, 3, 7]. Over the course of the disease a variety of non-motor symptoms may arise or can precede motor symptoms like depression, dementia, sleep disorders, anosmia, cognitive dysfunctions, psychosis etc. [10, 1, 23]. Even though, the precise pathophysiological cause of PD has not yet been discovered, the most significant biological finding is a rapid degeneration of dopaminergic cells in *substancia nigra pars compacta* [14].

Considering motor dysfunctions in people suffering from PD, in conjunction with complexity, proficiency and precision of handwriting performance, it is distinct that disrubted handwriting may be used as a significant biomarker for PD diagnosing [5, 30, 7]. With new technologies coming hand by hand with Health 4.0 systems we are able to acquire online handwriting signals, where a temporal information is added to x and y coordinates. Thus instead of quantifying PD micrographia by spatial features only, the use of digitalizing tablets gives us a new opportunity to quantify temporal, kinematic and dynamic manifestations of PD handwriting such as hesitations, pauses, and slow movement [3], which Letanneux et al. (2014) named PD dysgraphia [18].

The impact of many handwriting tasks in PD dysgraphia analysis has been explored, including simple (e. g. loops, circles, characters) as well as more complex ones (e. g. words, sentences, Archimedean spiral, figures) [7, 9, 8, 19, 25, 24]. Discrimination power of handwriting features is usually evaluated by correlation, classification and/or variance analysis. From the overview of related works (2015–now), which can be seen in Table II.1, it is obvious that kinematic features have irreplaceable place in PD dysgraphia analysis. Drotar et al. (2015, 2016) proved that combination of kinematic, pressure, energy or empirical mode decomposition (EMD) based features resulted in classification accuracy up to 89 % using several handwriting tasks [7, 9, 8]. Next, Kotsavasilogloua et al. (2017) achieved an average prediction accuracy of 91 % using simple horizontal lines and features describing a variability of the pen tip's velocity, a deviation from the horizontal plane, and the trajectory's entropy [16]. Some other works report even higher classification accuracies results (approximately 97 %), e.g. Loconsole et al. (2017) who used computer vision and electromyography signal processing techniques but applied on a very small dataset (4 PD and 7 HC). Thus, the reliability of those results may be untrustworthy.

Table II.1: Overview of related works focused on computerized analysis of PD dysgraphia

First author	Year	PD/HC	Handwriting task	Analysis	Features	Conclusions
Drotar [8]	2015	37/38	letters, words, sentences	differential analysis (SVM)	kinematic, temporal, spatial, entropy, EMD, signal energy	The highest classification accuracy after feature selection approach was 88.1 %.
Drotar [9]	2015	37/38	letters, words, sentences	differential analysis (SVM)	kinematic, temporal, spatial, entropy, EMD, pressure	Classification performance was at its peak with on-surface features (89.09 %).
Heremans [13]	2015	34/10	up/down strokes at varying amplitudes	ANOVA	writing amplitude and velocity	Significant difference between groups was in writing amplitude ($F(2.41) = 3.97; p = 0.03$).
Pereira [26]	2015	37/18	Archimedean spiral	differential an. (SVM, NB, OPF)	mean relative tremor and spatial parameters	The best results were obtained by NB classifier, that provided around 79 % classification accuracy.
Drotar [7]	2016	37/38	letters, words, Archimedean spiral, sentences	differential an. (SVM, K-NN, AdaBoost)	kinematic, temporal, spatial, entropy, EMD, pressure	Combining all exercises, SVM proved to be the best classifier with 82.5 % accuracy.
Heremans [12]	2016	30/15	repetitive cursive loops	ANOVA, correlation an.	writing amplitude and velocity	Medical scale and writing amplitude had significant correlation ($r = -0.40$).
Pereira [27]	2016	14/21	Archimedean spiral meander	differential an. (CNN, OPF)	pen-based features	The best result was obtained by CNN with 87.14 % recognition rate using meander task.
Kotsavasil. [16]	2017	24/20	horizontal lines	differential analysis (NB)	normalized velocity variability	Average classification accuracy was 91 % for unlabelled PD and HC data.
Loconsole [19]	2017	4/7	sentence, repetitive loops	differential analysis (ANN)	execution time and average speed, density ratio, height ratio	Highest classification accuracy (96.81 %) was achieved using all the extracted features.
Taleb [33]	2017	16/16	letters, waves, words	differential analysis (SVM)	kinematic, stroke, pressure, entropy, energy, EMD	The highest classification accuracy was 96.88 % for 12 kinematic and pressure features.
Moetesum [22]	2018	37/38	letters, words, Archimedean spiral, sentence, loops	differential analysis (SVM)	CNN based features	Extraction of features using CNN applied on raw handwriting data resulted in 83 % classification accuracy.

SVM – support vector machine; EMD – empirical mode decomposition; r_s – Spearman's correlation coefficient; K-NN – K-nearest neighbours; ANOVA – analysis of variance; NB – naïve Bayes classifier; OPF – optimum path forest; ANN – artificial neural network; CNN – convolutional neural networks; F and p corresponds to variables of F distribution; articles are sorted by the year of release and then alphabetically.

Another promising approach was published by Moetesum et al. (2018) who reached 83 % classification accuracy by employing convolutional neural networks (CNN) that were used to extract discriminating visual features from raw handwriting data.

The main goal of this work is to introduce an advanced approach of kinematic features calculation based on fractional order derivation (FDE) as a new methodology of PD dysgraphia analysis. We aim to:

- proof the potential of FDE in PD dysgraphia quantification employing classification analysis,
- evaluate discrimination power of the newly designed features when comparing the results with a baseline,
- identify a handwriting task that (in combination with the newly designed parameters) provides best results in terms of PD dysgraphia classification accuracy.

The rest of this paper is organized as follows: section II.2 describes cohort of patients and methodology, section II.3 includes achieved results, discussion can be found in section II.4 and finally, the conclusions are drawn in section II.5.

II.2 Dataset & Methods

II.2.1 Dataset

We used the Parkinson's disease handwriting database (PaHaW) [7] that consists 33 PD patients and 36 healthy controls (HC). Demographic and clinical data of the participants can be found in Table II.2. The participants were enrolled at the First Department of Neurology, St. Anne's University Hospital in Brno, Czech Republic. All participants reported Czech language as their native language and all participants were right-handed. The PD patients completed the tasks approximately 1 hour after their regular L-dopa medication. All participants signed an informed consent form approved by the local ethics committee.

II.2.2 Data Acquisition

PaHaW database [7] includes several handwriting tasks (see Fig. II.1), namely: Archimedean spiral; repetitive loops; letter *l*; syllable *le*; Czech words *les*, *lektorka*, *porovnat*, and *nepopadnout*; Czech sentence *Tramvaj dnes už nepojede.* During all handwriting tasks the participants were rested and seated in a comfortable position with possibility to look at pre-filled template. A digitizing tablet (Wacom Intuos 4M) was overlaid with an empty paper template and participants were allowed to repeat a task in case of some mistakes. Online handwriting signals were recorded with

Table II.2: Demographic and clinical data of participants

Parkinson's disease patients					
Gender	N	Age [y]	PD dur [y]	UPDRS V	LED [mg]
Female	17	71.76 ± 7.93	9.88 ± 5.27	2.18 ± 0.86	1146.03 ± 543.89
Male	16	66.50 ± 13.44	7.44 ± 4.04	2.31 ± 0.75	1673.38 ± 616.66
All	33	69.21 ± 11.10	8.70 ± 4.82	2.24 ± 0.80	1401.72 ± 630.71
Healthy controls					
Gender	N	Age [y]			
Female	17	61.59 ± 10.17			
Male	19	63.32 ± 13.14			
All	36	62.50 ± 11.70			

N – number; y – years; PD dur – PD duartion; UPDRS V – Unified Parkinson's disease rating scale, part V: Modified Hoehn & Yahr staging score [11]; LED – L-dopa equivalent daily dose [17].

$f_s = 150$ Hz sampling rate. Following time sequences were acquired: x and y coordinates – $x[t]$, $y[t]$; time-stamp – t; in-air/on-surface status – $b[t]$; pressure – $p[t]$; azimuth $az[t]$; and tilt $al[t]$.

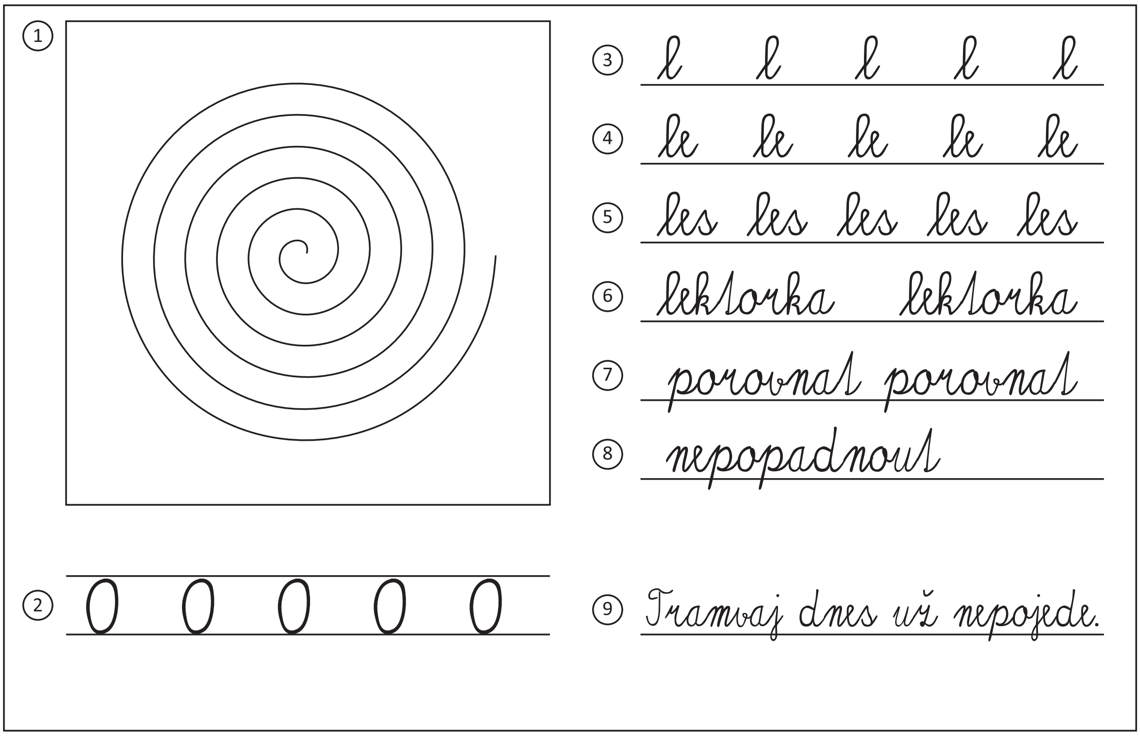

Fig. II.1: Filled template of the PaHaW database.

II.2.3 Fractional Order Derivative

The idea of this study is to use the FDE as a substitution of the conventional differential derivative during calculation of the basic kinematic features. There are several definitions of FDE, namely, the Riemann-Liouville, Caputo, and Grünwald-Letnikov formulations [34, 28, 15]. For the purpose of this study we used the Jonathan Hadida's FDE implementation, which follows the Grünwald-Letnikov approximation [32, 28]. A direct definition of the FDE $D^{\alpha}y(t)$ is based on finite differences of an equidistant grid in $[0, \tau]$. Assume that the function $y(\tau)$ satisfies some smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid [28]

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{II.1}$$

with

$$\tau_{k+1} - \tau_k = h \tag{II.2}$$

and using the notation of the finite differences

$$\frac{1}{h^{\alpha}}\Delta_h^{\alpha}y(t) = \frac{1}{h^{\alpha}}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^{\alpha} y(\tau_{n+1-v})\right), \tag{II.3}$$

where

$$c_v^{\alpha} = (-1)^{v-1}\binom{\alpha}{v}, \tag{II.4}$$

the Grünwald-Letnikov implementation is defined as:

$$D^{\alpha}y(t) = \lim_{h \to 0} \frac{1}{h^{\alpha}}\Delta_h^{\alpha}y(t), \tag{II.5}$$

where $D^{\alpha}y(t)$ means a derivative with order α of function $y(t)$, and h represents sampling lattice.

II.2.4 Handwriting Features

A wide range of handwriting features for analysis of PD dysgraphia is commonly used, but to demonstrate the impact of FDE, only basic on-surface kinematic features [7, 6, 21] extracted from all PaHaW tasks are considered. Feature set consists: *velocity*−rate at which a position of pen changes with time [mm/s]; *acceleration*−rate at which the velocity of pen changes with time [mm/s^2]; *jerk*−rate at which the acceleration of pen changes with time [mm/s^3]; and their horizontal and vertical variants. These features were extracted for different values of α going from 0.1 to 1.0 with 0.1 step. Consequently, statistical properties of the features were described using following statistics: mean, median, standard deviation (std), and maximum (max). Considering all combinations of tasks and features (with different FDE order), in total 5040 features were extracted.

II.2.5 Statistical Analysis

After feature extraction, univariate binary classification (PD/HC) model (stratified 7-fold cross-validation with 50 repetitions) based on random forests (RF) [2] was designed to evaluate a discrimination power of the features among all handwriting tasks. To eliminate non-significant features from results of univariate classification, Spearman's and Pearson's correlation analysis was performed (significance level of $p = 0.01$ was selected). Consequently, multivariate classification with the same classifier and the same cross-validation settings was performed in order to improve classification accuracy. To obtain the most appropriate combination of the features, the sequential floating forward selection (SFFS) algorithm was used [29]. Classification performance was evaluated by the Matthew's correlation coefficient [20], classification accuracy (ACC), sensitivity (SEN) and specificity (SPE).

II.3 Results

Univariate and multivariate classification analysis results are summarized in Table II.3. In the upper part of table the results of univariate analysis sorted by ACC are reported. Only 10 best features that achieved condition of significance ($p < 0.01$) were chosen. The best ACC (74.96 %) was obtained using horizontal acceleration with $\alpha = 0.6$ extracted from repetitive loops task. Nevertheless, based on the results, the most useful task is sentence (8/10 features with ACC around 74 %). Fig. II.2 displays dependence of ACC on FDE order for 3 most discriminative features extracted from this task. Dependence of average ACC for each α separately for XY, horizontal, vertical and altogether features extracted from all tasks is visualized in Fig. II.3. Regarding the multivariate classification analysis (bottom part of Table II.3), the best classification score (ACC = 89.81 %, SEN = 88.63 %, SPE = 90.87 %) was achieved using a combination of 5 kinematic features. The table contains information about RF performance as the features were gradually selected by the SFFS.

II.4 Discussion

With respect to the results of univariate analysis, previous hypothesis that FDE utilization in PD dysgraphia analysis may improve classification performance can be confirmed. Following the α values reported in Table II.3, it is evident that features calculated by FDE fully substitute conventional kinematic parameters based on the differential derivative (full derivative; $\alpha = 1$). The sentence appears to be the most suitable handwriting task in univariate classification analysis, where 8

Table II.3: Results of univariate and multivariate classification analysis

Univariate classification analysis

Feature	α	Task	ACC [%]	SEN [%]	SPE [%]	MCC	r_p	p_p	r_s	p_s
horizontal acceleration (mean)	0.6	repetitive loops	74.96	70.79	78.78	0.50	0.34	0.003821	0.52	0.000005
vertical velocity (max)	0.2	sentence	74.38	71.52	77.00	0.49	0.33	0.006085	0.44	0.000160
horizontal acceleration (mean)	0.5	repetitive loops	74.32	75.94	72.83	0.49	0.34	0.003785	0.50	0.000012
vertical jerk (max)	0.7	sentence	74.12	70.85	77.11	0.48	0.33	0.006086	0.44	0.000160
vertical velocity (max)	0.1	sentence	74.09	70.12	77.72	0.48	0.33	0.006086	0.44	0.000160
vertical acceleration (max)	0.6	sentence	74.00	70.24	77.44	0.48	0.33	0.006086	0.44	0.000160
vertical velocity (max)	0.8	sentence	74.00	70.36	77.33	0.48	0.33	0.006086	0.44	0.000160
vertical acceleration (max)	0.3	sentence	73.91	70.61	76.94	0.48	0.33	0.006086	0.44	0.000160
vertical jerk (max)	0.2	sentence	73.80	71.39	76.00	0.48	0.33	0.006086	0.44	0.000160
vertical jerk (max)	0.5	sentence	73.74	69.58	77.56	0.47	0.33	0.006086	0.44	0.000160

Multivariate classification analysis

Feature set			Model information				
Feature	α	Task	Features quantity	ACC [%]	SEN [%]	SPE [%]	MCC
velocity (max)	0.1	repetitive character *l*	1	76,25	73.07	79.85	0.5325
horizontal velocity (median)	0.5	repetitive word *lektorka*	2	80.40	78.28	82.81	0.6112
vertical velocity (median)	0.9	word *les*	3	82.99	78.46	87.74	0.6699
acceleration (median)	0.8	syllables *le*	4	88.66	88.37	88.64	0.7785
velocity (median)	0.1	word *porovnat*	5	**89.81**	88.63	90.87	0.8039

α – order of FDE; ACC – accuracy; SEN – sensitivity; SPE – specificity; r_p – Pearson's correlation coefficient; MCC – Matthew's correlation coefficient; r_s – Spearman's correlation coefficient; p_p – significance level of correlation (r_p); p_s – significance level of correlation (r_s)

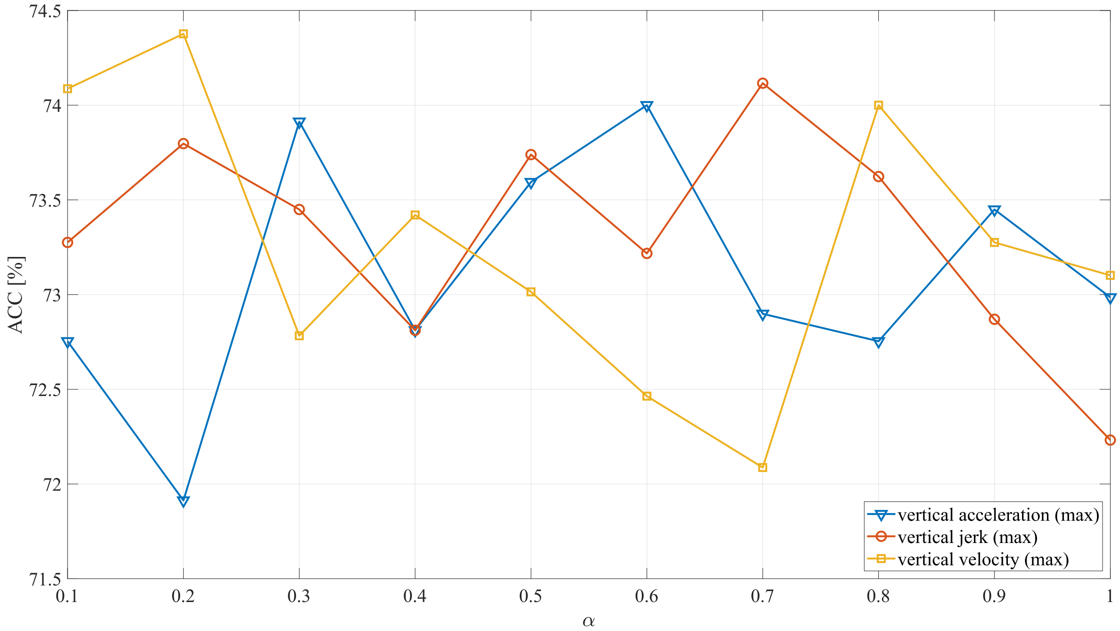

Fig. II.2: Dependence of classification accuracy on FDE order for 3 most discriminative features extracted from the sentence task.

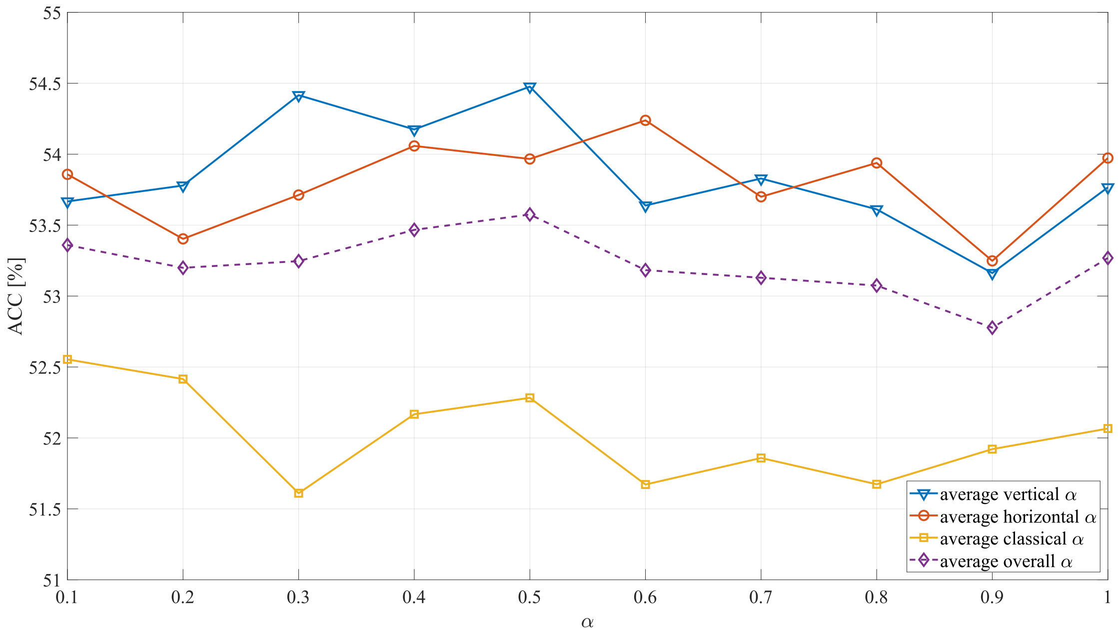

Fig. II.3: Dependence of average classification accuracy on FDE order separately for XY, horizontal, vertical and overall features.

out of 10 most discriminative features (ACC around 74 %) are extracted from this task. This finding is in line with results reported by Drotar et al. ([7]). The sentence provides good discriminative power because the PD dysgraphia symptoms have more space to emerge in comparison with others tasks of the PaHaW database. I. e. the task contains more on-surface/in-air transitions, it can capture decreasing amplitude of letters (micrographia), variations in handwriting kinematics, etc. We can conclude that the univariate approach described in this paper brings remarkable improvements giving very similar classification accuracy using only basic kinematic features in comparison with the baseline published by Drotar et al. (2016), where the authors reported ACC = 76.5 % for the sentence task using combination of several kinematic and pressure features.

The effect of FDE order on the classification performance (as visualized by Fig. II.2) has some local maxima for $\alpha \in < 0.2; 0.3 >$ and for $\alpha \in < 0.6; 0.8 >$. A decreasing character of ACC for α going from 0.8 towards the full derivation can be noticed. As can be seen in Fig. II.3 horizontal and vertical features generally provide higher classification accuracies when compared to the XY features. This can be also confirmed by the nature of the most discriminative features whereas all of them are horizontal or vertical. Considering, that the average classification accuracy based on the XY features is lower than the overall average, we conclude that the importance of separate movement directions analysis is high.

Next, classification performance was improved by approximately 15 % using the multivariate classification analysis. The best classification model contains only 5 features (providing ACC = 89.81 %, SEN = 88.63 % and SPE = 90.87 %) extracted from different handwriting tasks, including cursive letter "l", syllable, words and repetitive word. This higher-dimensional feature space points to complexity of handwriting and directs to the need of considering various aspects of deficits in PD during PD dysgraphia analysis. Based on the values of α, which are different from 1, we can confirm full utilization of FDE in multivariate classification analysis too. The best classification accuracy reported in the frame of PaHaW database is ACC = 89 % employing combination of kinematic and pressure features [9]. We reached the same accuracy omitting the pressure ones.

The reached accuracy is interesting from a clinical point of view too. It is well known that L-dopa medication has a positive effect on upper limb in PD, which means that theoretically PD dysgraphia in patients who are in their ON state should not be manifested significantly. Nevertheless, we proved that using advanced kinematic analysis we are able to differentiate HC and patients 1 hour after their regular L-dopa medication with almost 90 % accuracy.

Several other research teams published PD dysgraphia classification accuracies in range between 91 % and 97 %, however, analysing different datasets (with significantly lower number of samples) and extracting advanced handwriting features [16, 19, 33]. A relevant comparison is thus not possible.

II.5 Conclusion

This pilot study proves that application of FDE in quantitative PD dysgraphia analysis brings new promising and enhancing methodology of PD diagnosis. Based on the results, we are able to identify PD dysgraphia with almost 90 % accuracy using only 5 basic kinematic features extracted from a few handwriting tasks. We hypothesise that combination of the newly designed features with spatial, temporal and dynamic ones could bring even better results. Some improvements could be made in machine learning too. For instance application of boosting algorithms such as XGBoost would be beneficial. Finally, a lot can be further explored in the case of FDE, i. e. finer selection of FDE order and individual tuning of α for horizontal and vertical movement.

The limitation of this study is the size of database. As already mentioned, this study has a pilot character. To be able to generalize the results, bigger and multilingual datasets should be analysed.

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III Identification and Monitoring of Parkinson's Disease Dysgraphia Based on Fractional-Order Derivatives of Online Handwriting

Outline

Bibliographic Information

J. Mucha, J. Mekyska, Z. Galaz, M. Faundez-Zanuy, K. Lopez-de-Ipina, V. Zvoncak, T. Kiska, Z. Smekal, L. Brabenec and I. Rektorova. Identification and monitoring of Parkinson's disease dysgraphia based on fractional-order derivatives of online handwriting. In *Applied Sciences*, 8(12), 2566. Multidisciplinary Digital Publishing Institute, 2018. `doi:/10.3390/app8122566`.

Author's Contribution

The author proposed the concept of the paper, surveyed related works, co-proposed a new parametrization method, co-designed the methodology, performed analysis, validated and co-investigated the results, and assisted with data curation. He also prepared the original draft and worked on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

Parkinson's disease dysgraphia affects the majority of Parkinson's disease (PD) patients and is the result of handwriting abnormalities mainly caused by motor dysfunctions. Several effective approaches to quantitative PD dysgraphia analysis, such as online handwriting processing, have been utilized. In this study, we aim to deeply explore the impact of advanced online handwriting parameterization based on fractional-order derivatives (FD) on the PD dysgraphia diagnosis and its monitoring. For this purpose, we used 33 PD patients and 36 healthy controls from the PaHaW (PD handwriting database). Partial correlation analysis (Spearman's and Pearson's) was performed to investigate the relationship between the newly designed features and patients' clinical data. Next, the discrimination power of the FD features was evaluated by a binary classification analysis. Finally, regression models were trained to explore the new features' ability to assess the progress and severity of PD. These results were compared to a baseline, which is based on conventional online handwriting features. In comparison with the conventional parameters, the FD handwriting features correlated more significantly with the patients' clinical characteristics and provided a more accurate assessment of PD severity (error around 12%). On the other hand, the highest classification accuracy (ACC = 97.14%) was obtained by the conventional parameters. The results of this study suggest that utilization of FD in combination with properly selected tasks (continuous and/or repetitive, such as the Archimedean spiral) could improve computerized PD severity assessment.

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III.1 Introduction

As a second most common neurodegenerative disorder, Parkinson's disease (PD) is expected to impose an increasing social and economic burden on societies as populations age [5]. Its prevalence rate is estimated to approximately 1.5% for people aged over 65 years [6]. The risk of being affected by PD strongly increases with age, and, in the next 15 years, the incidence of PD is expected to be doubled [45, 20]. The rapid degeneration of dopaminergic cells in the substantia nigra pars compacta [21] arose as the most significant biological finding associated with the disease, but the exact pathophysiological cause of PD has not yet been discovered. PD cardinal motor symptoms involve bradykinesia (slowness of movement), tremor at rest, rigidity, gait impairment, and postural instability [16, 9, 13]. A variety of non-motor symptoms may emerge as well—for instance, cognitive impairment, dementia, depression, sleep disorders, or anxiety [16, 7, 36].

Handwriting requires cognitive, perceptual, and fine motor abilities. In conjunction with motor dysfunctions in people suffering from PD, it has been proven that disrupted handwriting may be used as a significant biomarker for PD diagnosis [10, 43]. Micrographia, which is associated with the progressive decrease in letters' amplitude, is the most commonly observed handwriting abnormality in patients with PD [52, 33]. Moreover, according to McLennan et al. [33], in approximately 5% of PD patients, micrographia may be observed even before the onset of the cardinal motor symptoms.

The recent advantage of new technologies coming hand-in-hand with Health 4.0 systems enables the acquisition of online handwriting signals, where temporal information is added to the x and y position. Therefore, by using a digitizing tablet, the analysis is not limited to spatial features which mainly quantify PD micrographia. In addition, we are able to quantify temporal, kinematic, and dynamic manifestations of PD dysgraphia, such as hesitations, pauses, and slow movement [9], which cannot be studied objectively using a classical paper-and-pen method. Due to this complexity, Letanneux et al. [27] started to refer to these manifestations using the generalized term PD dysgraphia.

Several research teams have explored the impact of quantitative PD dysgraphia analysis utilizing simple handwriting/drawing tasks (e.g., separate characters, a combination of two or three characters, repetitive loops, circles), as well as more complex ones (e.g., words, sentences, figures, 3D objects, and the Archimedean spiral) [13, 15, 14, 28, 38, 37]. An overview of recent related works (2015–present) can be seen in Table III.1. Most of them confirm the irreplaceability of kinematic features in PD dysgraphia analysis. Additionally, the researchers usually employ temporal, spatial, and dynamic features. Some more advanced parameters are reported too. For instance, Drotar et al. [13, 15, 14] demonstrated a combination of kinematic, pressure, energy, or empirical mode decomposition (EMD)-based features that resulted in a classification accuracy of up to 89% using several handwriting tasks. Kotsavasilogloua et al. [25] achieved an average prediction accuracy of 91% using simple horizontal lines and features describing the variability in the pen tip's velocity, a deviation from the horizontal plane, and the trajectory's entropy. Other works report even higher classification accuracies (approximately 97%), e.g., Loconsole et al. [28], who used computer vision and electromyography signal processing techniques, or Taleb et al. [49], who used a combination of features related to the correlation between kinematic and pressure characteristics (but, in this case, applied to a very small dataset). Another promising approach was published by Moetesum et al. [35], who reached an 83% classification accuracy by employing convolutional neural networks (CNN) that were used to extract discriminating visual features from handwriting data transformed into the offline mode. In 2018, Impedovo et al. reported the results of a study focused only on the early stages of PD; the best accuracy was 74.76% for a combination of three handwriting tasks. Finally, in our previous work [37], we proposed a new approach of advanced kinematic feature extraction that utilizes fractional-order derivatives (FD). This approach increased the classification accuracy by 10% (72.39%) for Archimedean spiral tasks in comparison with the baseline [37].

Although the authors of the previously mentioned studies reported high classification accuracies, further signal processing and machine learning pipeline improvements are expected to make the differential analysis even more accurate. One possible approach could involve an advanced feature extraction methodology based on fractional calculus (FC) [4, 23], which enables the use of an arbitrary order of derivatives and/or integrals. Generally, FC has many applications in different fields of science [42, 53, 44]. For instance, it has been advantageously used during the modeling of different diseases, such as human immunodeficiency virus (HIV) [2] and malaria [41]. In addition, FC-based analytical tools have outperformed classical techniques in geology [30, 29], economics and finance [46, 3], etc. Moreover, in our recent paper [37], we identified a high potential for the use of FC in the kinematic analysis of PD drawings. Based on these preliminary results, we assume that FD-based handwriting features may bring improvements to PD diagnosis and assessment. In the frame of this article, we would like to go further and deeply explore the impact of FD on the PD dysgraphia diagnosis and its monitoring. More specifically, we aim to:

- investigate the relationship between newly designed FD handwriting features and a patient's clinical data and compare these results with a baseline (i.e., results based on conventional parameters),

Table III.1: Overview of related works focused on computerized analysis of Parkinson's disease (PD) dysgraphia.

First Author	Year	PD/HC	Handwriting Task	Analysis	Features	Conclusions
Drotar * [14]	2015	37/38	letters, words, sentences	differential analysis (SVM)	kinematic, temporal, spatial, entropy, EMD, signal energy	The highest classification accuracy after feature selection approach was 88.13%.
Drotar * [15]	2015	37/38	letters, words, sentences	differential analysis (SVM)	kinematic, temporal, spatial, entropy, EMD, pressure	Classification performance was at its peak with on-surface features equal to AUC = 89.09%.
Heremans [19]	2015	34/10	up/down strokes at varying amplitudes	ANOVA	spatial and kinematic	Significant difference between groups was in spatial ($F(2.41) = 3.97; p = 0.03$).
Pereira [39]	2015	37/18	Archimedean spiral	differential an. (SVM, NB, OPF)	mean relative tremor and spatial parameters	The best results were obtained by NB classifier that provided around 79% classification accuracy.
Drotar * [13]	2016	37/38	letters, words, Archimedean spiral, sentences	differential an. (SVM, K-NN, ADA)	kinematic, temporal, spatial, entropy, EMD, pressure	Combining all exercises, SVM proved to be the best classifier with 82.5% accuracy.
Heremans [18]	2016	30/15	repetitive cursive loops	ANOVA, correlation an.	writing amplitude and velocity	PD dysgraphia is more severe in patients with freezing of gait.
Pereira [40]	2016	14/21	Archimedean spiral, meander	differential an. (CNN, OPF)	pen-based features	The best result was obtained by CNN with 87.14% classification accuracy using meander task.
Kotsavasil [25]	2017	24/20	horizontal lines	differential analysis (NB)	kinematic	Average classification accuracy was 91%.
Loconsole [28]	2017	4/7	sentence, repetitive loops	differential analysis (ANN)	temporal, kinematic, spatial	Highest classification accuracy (96.81%) was achieved using all the extracted features.
Taleb [49]	2017	16/16	letters, waves, words	differential analysis (SVM)	kinematic, stroke, pressure, entropy, energy, EMD	The highest classification accuracy was 96.88% for 12 kinematic and pressure features.
Moetesum * [35]	2018	37/38	Archimedean spiral, letters, words, sentence, loops	differential analysis (SVM)	CNN-based features	Extraction of features using CNN applied on raw handwriting data resulted in 83% classification accuracy.
Mucha * [37]	2018	30/36	Archimedean spiral	differential analysis (RF, SVM)	fractional derivatives based kinematic features	Improvement of classification accuracy by 10% (72.38%) in comparison to the baseline.
Impedovo * [22]	2018	37/38	Archimedean spiral letters, words, sentence	differential an. (RF, SVM, K-NN, NB, LDA, ADA)	kinematic, temporal, spatial, entropy, EMD, pressure	Analysis focused on PD diagnosis at earlier stages resulted in 74.76% classification accuracy.

SVM—support vector machine; EMD—empirical mode decomposition; K-NN—K-nearest neighbors; ANOVA—analysis of variance; NB—naïve Bayes classifier; OPF—optimum path forest; ANN—artificial neural network; CNN—convolutional neural network; RF—random forests; LDA—Linear Discriminant Analysis; ADA—AdaBoost; AUC—area under the receiver operating characteristics (ROC) curve; articles are sorted by the year of release and then alphabetically; * analyzes performed on the same database (Parkinson's disease handwriting database (PaHaW) [13]).

- evaluate the discrimination power of the FD features in terms of binary classification accuracy and compare the results to the baseline,
- use the newly designed features to establish regression models that will estimate the severity of PD and compare its performance to that of a baseline.

The rest of this paper is organized as follows: Section III.2 describes the cohort of patients and the methodology, and Section III.3 includes the results. A discussion is presented in Section III.4, and, finally, conclusions are drawn in Section III.5.

III.2 Materials and Methods

III.2.1 Dataset

For the purpose of this work, the Parkinson's disease handwriting database (PaHaW) [13], which consists of multiple handwriting/drawing samples from 37 PD patients and 38 age- and gender-matched healthy controls (HC), was used. Since the Archimedean spiral drawing task is missing for some participants, we reduced the analyzed cohort to 33 PD patients and 36 HC. Demographic and clinical data of the participants can be found in Table III.2. The participants were enrolled at the First Department of Neurology, St. Anne's University Hospital in Brno, Czech Republic. All participants reported the Czech language as their native language and were right-handed. The patients completed their tasks approximately 1 h after their regular dopaminergic medication (L-dopa). All participants signed an informed consent form approved by the local ethics committee. Unified Parkinson's disease rating scale, part V (UPDRS V): Modified Hoehn and Yahr staging score [17], was used to assess clinical symptoms of PD. In the frame of this work, the duration of the disease was considered as well. Descriptive visualization (histograms, regression, and residual plots) of the clinical data for the subjects participating in this study can be seen in Figure III.1.

Table III.2: Demographic and clinical data of the enrolled participants.

Gender	**N**	**Age [years]**	**PD dur [years]**	**UPDRS V**	**LED [mg/day]**
		Parkinson's disease patients			
Females	17	71.76 ± 10.93	9.88 ± 5.27	2.18 ± 0.86	1146.03 ± 543.89
Males	16	66.50 ± 13.44	7.44 ± 4.04	2.31 ± 0.75	1673.38 ± 616.66
All	33	69.21 ± 11.10	8.70 ± 4.82	2.24 ± 0.80	1401.72 ± 630.71
		Healthy controls			
Females	17	61.59 ± 10.17	-	-	-
Males	19	63.32 ± 13.14	-	-	-
All	36	62.50 ± 11.70	-	-	-

PD—Parkinson's disease; N—number of subjects; PD dur—PD duration; UPDRS V—Unified Parkinson's disease rating scale, part V: Modified Hoehn and Yahr staging score [17]; LED—L-dopa equivalent daily dose [26].

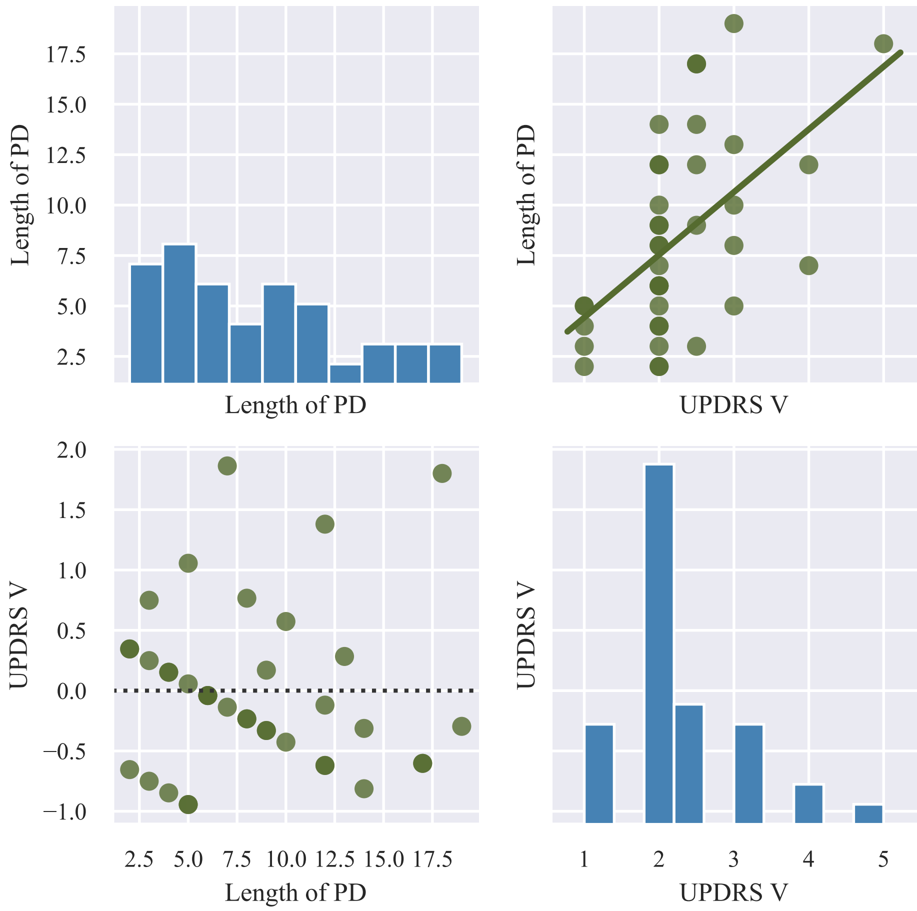

Fig. III.1: Descriptive graphs of patients' clinical characteristics: Unified Parkinson's disease rating scale (UPDRS V) and Parkinson's disease (PD) duration (in years). Histograms are visualized on the diagonal. A scatterplot with a line fitted using linear regression is visualized in the top-right corner. Residuals of the trained linear model are visualized in the bottom-left corner.

III.2.2 Data Acquisition

The PaHaW database [13] includes nine different handwriting tasks written in the Czech language. Their description and translation to English can be found in Table III.3. During all handwriting tasks, the participants were rested and seated in a comfortable position with the possibility to look at the prefilled template (see Figure III.2). A digitizing tablet (Wacom Intuos 4M, Wacom, Kazo, Saitama, Japan) was overlaid with an empty paper template and participants were asked to perform all tasks using a special Wacom inking pen that gave the patients immediate visual feedback. Online handwriting signals were recorded with a sampling frequency of $f_s = 150\,\text{Hz}$. The following time sequences were acquired: x and y coordinates ($x[t]$, $y[t]$); time-stamp (t); in-air/on-surface (on-surface movement is a movement of a pen when its tip is touching the surface, e.g., paper (i.e., it provides the information about the pen writing/drawing on the paper); vice versa, in-air movement is a movement of a pen when its tip is up to 1.5 cm above the surface [48, 1]) status ($b[t]$); pressure ($p[t]$); azimuth ($az[t]$); and altitude ($al[t]$).

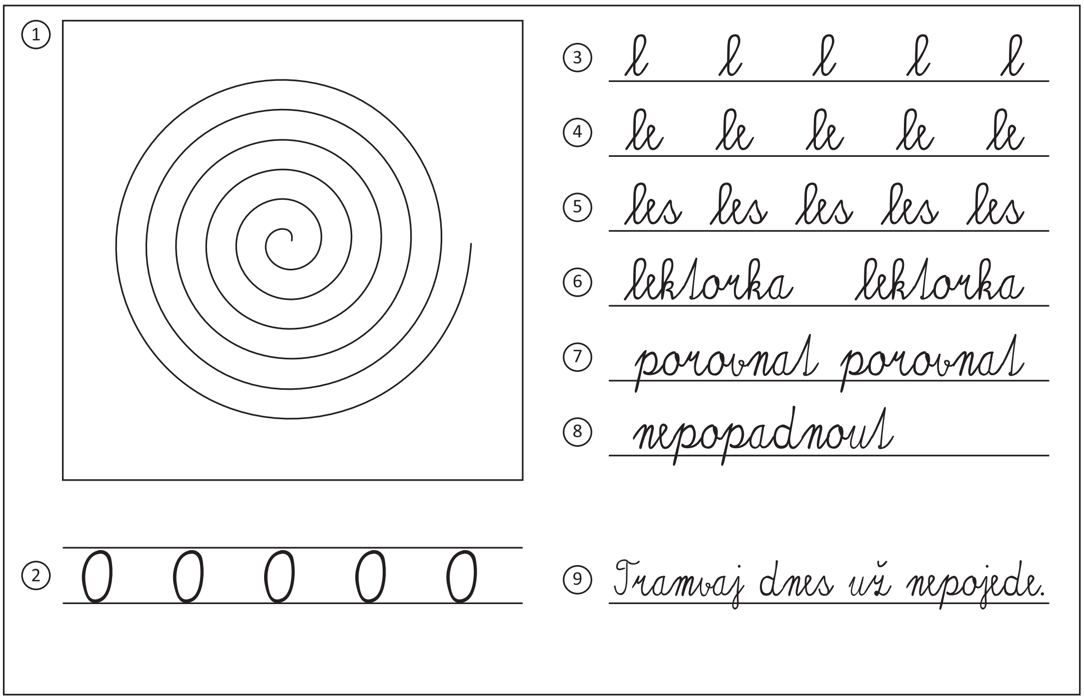

Fig. III.2: Filled template of the PaHaW database.

Table III.3: Description of the PaHaW handwriting tasks.

N	Task	Czech (Original)	English (Translation)
1	Archimedean spiral	-	-
2	repetitive loops	-	-
3	letter	l	l
4	syllable	le	le
5	word	les	forest
6	word	lektorka	lecturer
7	word	porovnat	compare
8	word	nepopadnout	not grasped
9	sentence	Tramvaj dnes už nepojede.	The tram will no longer go today.

III.2.3 Feature Extraction

The main goal of this work is to compare a set of commonly used kinematic features with newly proposed FD-based features in terms of quantitative PD dysgraphia analysis. All of the handwriting features were computed using both on-surface as well as in-air movements. The two movements were quantified separately using *velocity* (rate at which the position of the pen changes with time [mm/s]), *acceleration* (rate at which the velocity of the pen changes with time [mm/s^2]), *jerk* (rate at which the acceleration of the pen changes with time [mm/s^3]), and their horizontal and vertical variants [13, 12, 34]. FD-based features were extracted for different values of α. In the frame of this work, α ranging from 0.1 to 1.0 with a step of 0.1 was used. Subsequently, the statistical properties of the computed handwriting features were described using the mean, median, standard deviation (std), and maximum (max). Finally, all of the extracted features were divided into nine different feature sets according to the type of the movement (on-surface, in-air, and combined) and the calculation approach, i.e., the type of feature (FD-based, conventional, and combined). For more information, see Table III.4.

Table III.4: Feature sets matrix.

Movement	**FD (Count)**	**Conventional (Count)**	**Together (Count)**
on-surface	4536	618	5154
in-air	2916	404	3320
together	7452	1022	8474

Fractional-Order Derivatives

Utilization of the FD as a substitution for the conventional differential derivative during calculation of the basic kinematic features provides a new advanced approach. The advantage of FDs is in their wide range of settings and many different approaches to approximation, e.g., Riemann–Liouville, Caputo, or Grünwald–Letnikov formulations [50, 42, 24]. For the purpose of this work, Jonathan Hadida's FD Matlab implementation was used following the Grünwald–Letnikov approximation [47, 42]. A direct definition of the FD $D^\alpha y(t)$ is based on the finite differences of an equidistant grid in $[0, \tau]$, assuming that the function $y(\tau)$ satisfies certain smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid [42],

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{III.1}$$

with

$$\tau_{k+1} - \tau_k = h \tag{III.2}$$

and using the notation of finite differences

$$\frac{1}{h^\alpha}\Delta_h^\alpha y(t) = \frac{1}{h^\alpha}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^\alpha y(\tau_{n+1-v})\right), \tag{III.3}$$

where

$$c_v^\alpha = (-1)^{v-1}\binom{\alpha}{v}. \tag{III.4}$$

The Grünwald–Letnikov implementation is defined as

$$D^\alpha y(t) = \lim_{h\to 0} \frac{1}{h^\alpha} \Delta_h^\alpha y(t), \tag{III.5}$$

where $D^\alpha y(t)$ denotes a derivative with order α of function $y(t)$, and h represents a sampling lattice.

III.2.4 Statistical Analysis

Prior to providing a description of the analytical setup, it is important to note that the effect of well-known confounding factors, also known as covariates, was controlled for in all of the analytical steps described below. In the frame of this work, we controlled for the effect of participants' age, gender, and L-dopa [26] (dopaminergic medication).

To assess the strength of the relationship between the computed handwriting features and patient's clinical data (UPDRS V and PD duration), we computed the partial Pearson's correlation coefficient (assessment of a linear relationship), as well as the partial Spearman's correlation coefficient (assessment of a monotonic relationship). With this approach, we aimed to identify the handwriting features that are significantly correlated with the clinical measures under focus and also to compare the FD features with conventional ones. A significance level of correlation (p) of 0.05 was selected for both of the correlation types. Only the results with a p-value below the significance level in both correlation coefficients were considered statistically significant.

Next, to evaluate and compare the power of the handwriting features to discriminate PD patients and HC, multivariate binary classification analysis was performed. For this purpose, state-of-the-art gradient boosted trees were employed. Specifically, we used the famous XGBoost algorithm [8]. The XGBoost algorithm was chosen for its ability to achieve a good performance, even for small datasets; its inherent robustness to outliers; its ability to model complex interdependencies in the data; and also its recent successes in the field of machine learning (e.g., the winning algorithm in many `www.kaggle.com` competitions). To train and evaluate the models, we used the following supervised learning setup: stratified 10-fold cross-validation with 20 repetitions. The performance of the trained classification models was evaluated by Matthew's correlation coefficient (MCC) [32], classification accuracy (ACC), sensitivity (SEN), and specificity (SPE), which are defined as follows:

$$\mathrm{MCC} = \frac{\mathrm{TP}\times\mathrm{TN} - \mathrm{FP}\times\mathrm{FN}}{\sqrt{(\mathrm{TP}+\mathrm{FP})(\mathrm{TP}+\mathrm{FN})(\mathrm{TN}+\mathrm{FP})(\mathrm{TN}+\mathrm{FN})}}, \tag{III.6}$$

$$\text{ACC} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}} \cdot 100\,[\%], \tag{III.7}$$

$$\text{SEN} = \frac{\text{TP}}{\text{TP} + \text{FN}} \cdot 100\,[\%], \tag{III.8}$$

$$\text{SPE} = \frac{\text{TN}}{\text{TN} + \text{FP}} \cdot 100\,[\%], \tag{III.9}$$

where TP is the number of true positives, TN is the number of true negatives, FP is the number of false positives, and FN is the number false negatives.

Finally, to evaluate and compare the power of the handwriting features' ability to predict the values of the selected clinical characteristics (UPDRS V and PD duration), multivariate regression analysis was performed. For this purpose, the same boosting tree algorithm (XGBoost) and the supervised learning setup were used. The performance of the trained regression models was evaluated by the mean absolute error (MAE), root mean square error (RMSE), and estimated error rate (EER), which are defined as follows:

$$\text{MAE} = \frac{1}{n}\sum_{i=1}^{n}|y_i - \hat{y}_i|, \tag{III.10}$$

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}, \tag{III.11}$$

$$\text{EER} = \frac{1}{n \cdot r}\sum_{i=1}^{n}|y_i - \hat{y}_i| \cdot 100\,[\%], \tag{III.12}$$

where y_i represents the true label of the ith observation, $\hat{y}_i$ denotes the predicted label of the ith observation, n is the number of observations, and r is the range of the values of the predicted clinical characteristic (not the range that can be theoretically reached, but the actual range of the values in the dataset). Therefore, the EER describes a percentage of error predictions in regard to the statistical properties of the data.

III.3 Results

In Table III.5, the results of partial correlation analysis between the handwriting features (FD-based features, conventional features) and patients' clinical characteristics (UPDRS V, PD duration) are summarized. The table shows the five best features according to Spearman's correlation coefficient for each movement (on-surface, in-air). In the case of UPDRS V (on-surface movement), the following FD-based features achieved a statistical significance of correlation: the median of jerk ($\alpha = 0.3$, $\alpha = 0.4$) and horizontal velocity ($\alpha = 0.1$) for the repetitive letter *l*, the mean of vertical acceleration ($\alpha = 0.7$) for repetitive loops, and the standard deviation

Table III.5: Results of partial correlation analysis between handwriting features and clinical data.

UPDRS V								
FD on-suface							Conventional on-surface	
feature name	α	task	r_p	r_s	r_s	r_p	task	feature name
jerk (median)	0.3	r. letters l	0.37 *	0.48 **	−0.45 *	−0.24	r. letters le	h. jerk (max)
jerk (median)	0.4	r. letters l	0.43 *	0.46 *	−0.43 *	−0.2	r. letters le	velocity (max)
h. velocity (std)	0.1	r. letters l	−0.42 *	−0.41 *	−0.42 *	0.25	r. letters l	h. jerk (max)
v. acceleration (mean)	0.7	r. loops	0.48 **	0.40 *	−0.42 *	−0.16	r. letters l	h. velocity (max)
v. velocity (std)	0.3	sentence	0.40 *	0.40 *	−0.41 *	−0.15	letter l	h. velocity (max)
FD in-air							Conventional in-air	
feature name	α	task	r_p	r_s	r_s	r_p	task	feature name
v. velocity (median)	0.9	sentence	0.44 *	0.53 **	0.43 *	0.28	r. word lektorka	acceleration (mean)
v. velocity (median)	0.8	sentence	0.40 *	0.52 **	−0.37 *	−0.31	word porovnat	h. jerk (max)
h. velocity (median)	0.5	r. letters le	−0.38 *	−0.49 **	0.36 *	0.25	r. letters l	v. velocity (median)
v. jerk (median)	0.3	r. letters le	−0.43 *	−0.49 **	0.35	0.41 *	r. letters le	h. velocity (median)
v. velocity (median)	0.7	sentence	0.37 *	0.48 **	0.35	0.19	r. word lektorka	acceleration (median)
PD Duration								
FD on-surface							Conventional on-surface	
feature name	α	task	r_p	r_s	r_s	r_p	task	feature name
velocity (max)	0.1	spiral	0.54 **	0.55 **	−0.46 *	−0.40 *	r. letters l	h. velocity (max)
acceleration (max)	0.8	spiral	0.54 **	0.54 **	−0.40 *	−0.37 *	r. letters l	h. jerk (max)
acceleration (max)	0.6	spiral	0.54 **	0.54 **	−0.38 *	−0.37 *	r. letters l	velocity (max)
acceleration (max)	0.2	spiral	0.54 **	0.54 **	0.46 **	0.34	spiral	v. velocity (mean)
acceleration (max)	0.7	spiral	0.54 **	0.53 **	0.40 *	0.14	r. loops	h. acceleration (mean)
FD in-air							Conventional in-air	
feature name	α	task	r_p	r_s	r_s	r_p	task	feature name
jerk (median)	0.4	sentence	−0.37 *	−0.49 **	−0.44 *	−0.38 *	word lektorka	h. jerk (median)
jerk (max)	0.1	r. word les	0.57 **	0.46 *	0.38 *	0.40 *	word nepopad.	velocity (max)
jerk (max)	0.3	r. word les	0.57 **	0.45 *	0.37 *	0.42 *	word lektorka	h. n. jerk (mean)
velocity (max)	0.1	r. word les	0.57 **	0.45 *	−0.47 **	−0.13	r. word lektorka	h. velocity (mean)
jerk (max)	0.2	r. word les	0.57 **	0.45 *	−0.42 *	−0.13	word nepopad.	h. velocity (mean)

α—order of FD; r_p—Pearson's correlation coefficient; r_s—Spearman's correlation coefficient; v.—vertical; h.—horizontal; r.—repetitive task; *—$p < 0.05$; **—$p < 0.01$; rows are ordered by the absolute value of Spearman's correlation coefficient.

of the vertical velocity ($\alpha = 0.3$) for the sentence. The following conventional features achieved a statistical significance of correlation (p-value of only one of the coefficients was below the threshold): the maximum of horizontal jerk and velocity for the repetitive letters *le*, the maximum of horizontal jerk and horizontal velocity for the repetitive letter *l*, and the maximum of horizontal velocity for the letter *l*. Regarding UPDRS V (in-air movement), the following FD-based features achieved a statistical significance of correlation: the median of vertical velocity ($\alpha = 0.9$, $\alpha = 0.8$, $\alpha = 0.7$) for the sentence and the median of horizontal velocity ($\alpha = 0.5$) and vertical jerk ($\alpha = 0.3$) for the repetitive letters *le*. The following conventional features achieved a statistical significance of correlation (p-value of only one of the coefficients was below the threshold): the mean of acceleration for the repetitive word *lektorka*, the maximum of horizontal jerk for the word *porovnat*, the median of the vertical velocity for the repetitive letter *l*, and the median of the horizontal velocity of the repetitive letters *le*.

For PD duration (on-surface movement), the following FD-based features achieved a statistical significance of correlation (of note: all of these features satisfied the stronger threshold for statistical significance of correlation $p < 0.01$): the maximum of the velocity ($\alpha = 0.1$) and acceleration ($\alpha = 0.8$, $\alpha = 0.7$, $\alpha = 0.6$, $\alpha = 0.2$) for the Archimedean spiral. The following conventional features achieved a statistical significance of correlation (p-value of only one of the coefficients was below the threshold): the maximum of horizontal velocity, horizontal jerk, and velocity for the repetitive letter *l*; the mean of the vertical velocity for the Archimedean spiral; and the mean of horizontal acceleration for repetitive loops. For PD duration (in-air movement), the following FD-based features achieved a statistical significance of correlation: the median of jerk ($\alpha = 0.4$) for sentence, the maximum of jerk ($\alpha = 0.1$, $\alpha = 0.2$, $\alpha = 0.3$) and velocity ($\alpha = 0.1$) for repetitive word *les*. The following conventional features achieved a statistical significance of correlation (p-value of only one of the coefficients was below the threshold): the median and mean of horizontal jerk for the word *lektorka*, the maximum of the velocity for the word *nepopadnout*, and the mean of horizontal velocity for the repetitive word *lektorka* and the word *nepopadnout*.

The results of the multivariate binary classification analysis are summarized in Table III.6. In total, we built and evaluated nine different classification models. These models were selected according to the following criteria: movement type (on-surface, in-air, all), feature type (FD features, conventional features, all). We built models based on the combinations of these criteria as well. For more information, see Table III.4.

With respect to the classification performance, the highest MCC achieved was 0.95 was for eight out of the total nine feature sets (with the exception being the feature set composed of conventional handwriting features computed for the on-surface movements). An interesting fact to note is that for all models based on conventional handwriting features, only a single feature was capable of providing the classification models with such a high discrimination power. In terms of the specific features important for the trained models, the following feature importances were returned by the models (feature importance quantifies the relative importance of the features in the ensemble of the trained XGBoost model [8]; therefore, the higher the value of the feature importance, the more important the feature for the prediction of the dependent variable): conventional on-surface (horizontal jerk (median) of repetitive loops), conventional in-air (horizontal velocity (median) of the sentence), conventional together (horizontal velocity (median) of the sentence),

Table III.6: Results of multivariate binary classification analysis (PD/HC).

Feature Set	**MCC**	**ACC** [%]	**SEN** [%]	**SPE** [%]	**Feat**
conventional on-surface	0.83 ± 0.18	91.19 ± 9.65	93.00 ± 15.52	70.00 ± 0.46	1
conventional in-air	0.95 ± 0.10	**97.14 ± 5.71**	95.50 ± 9.07	100.00 ± 0.00	1
conventional together	0.95 ± 0.11	**97.14 ± 5.71**	95.50 ± 9.07	100.00 ± 0.00	1
FD on-surface	0.95 ± 0.12	87.14 ± 13.48	82.00 ± 21.24	90.00 ± 30.00	1
FD in-air	0.95 ± 0.13	81.43 ± 12.86	71.50 ± 30.83	60.00 ± 48.99	3
FD together	0.95 ± 0.14	81.43 ± 15.71	69.50 ± 32.13	70.00 ± 45.83	2
all on-surface	0.95 ± 0.15	88.33 ± 14.06	89.00 ± 22.11	70.00 ± 45.83	2
all in-air	0.95 ± 0.16	**97.14 ± 5.71**	95.50 ± 9.07	100.00 ± 0.00	1
all together	0.95 ± 0.17	**97.14 ± 5.71**	95.50 ± 9.07	100.00 ± 0.00	1

MCC—Matthew's correlation coefficient; ACC—accuracy; SEN—sensitivity; SPE—specificity; feat.—number of features important for the trained model (i.e., feature importance of the feature > 0.0); The feature importances, as well as the exact names of these features, are summarized in the text.

FD on-surface (jerk (max) $\alpha = 0.3$ of the letters *le*), FD in-air (vertical acceleration (mean) $\alpha = 0.6$ of the word *nepopadnout* (FI $= 0.33$), horizontal jerk (mean) $\alpha = 0.9$ of the word *nepopadnout* (FI $= 0.33$), horizontal jerk (mean) $\alpha = 0.2$ of the repetitive word *lektorka* (FI $= 0.33$)), FD together (jerk (max) $\alpha = 0.3$ of the letters *le* (on-surface; FI $= 0.67$), horizontal jerk (mean) $\alpha = 0.9$ of the word *nepopadnout* (in-air; FI $= 0.33$)), all on-surface (horizontal jerk (median) of repetitive loops (FI $= 0.50$), jerk (max) $\alpha = 0.3$ of the letters *le* (FI $= 0.50$)), all in-air (horizontal velocity (median) of the sentence), and all together (horizontal velocity (median) of the sentence (in-air)).

The results of multivariate regression analysis are summarized in Table III.7. For this purpose, we used UPDRS V and PD duration as our target variables. As in the case of binary classification, we built and evaluated nine different regression models according to the same criteria. For each of the rating scales, the table shows the results achieved using the trained models and the associated feature importance values. All obtained results are discussed in the following section.

Considering EER as our performance evaluation metric, the following results are worth pointing out. In the case of UPDRS V, the lowest EER was achieved using a single FD-based feature—specifically, the standard deviation of vertical velocity ($\alpha = 0.1$) computed for the on-surface movements ($12.51 \pm 7.55\%$). The same feature was selected when both FD and conventional features were considered while building the model. In general, all models achieved an EER of around 12–13%. In comparison with the conventional features, the FD-based features performed better, with a difference of about 1%. In terms of the specific features important for the trained models, the following feature importances were returned by the models:

Table III.7: Results of regression analysis for clinical data.

Feature Set	**MAE**	**RMSE**	**EER** [%]	**Feat**
		UPDRS V		
conventional on-surface	0.59 ± 0.29	0.71 ± 0.41	13.82 ± 6.71	1
conventional in-air	0.60 ± 0.30	0.72 ± 0.42	14.01 ± 6.98	1
conventional together	0.60 ± 0.31	0.73 ± 0.42	14.05 ± 6.90	1
FD on-surface	0.60 ± 0.32	0.65 ± 0.45	**12.51 ± 7.55**	1
FD in-air	0.60 ± 0.33	0.68 ± 0.43	13.49 ± 7.29	1
FD together	0.60 ± 0.34	0.66 ± 0.45	13.06 ± 7.55	2
all on-surface	0.60 ± 0.35	0.65 ± 0.45	**12.51 ± 7.55**	1
all in-air	0.60 ± 0.36	0.71 ± 0.43	13.72 ± 7.36	1
all together	0.60 ± 0.37	0.66 ± 0.45	13.06 ± 7.55	2
		PD duration		
conventional on-surface	4.29 ± 0.94	5.03 ± 1.09	24.52 ± 5.39	18
conventional in-air	4.91 ± 1.38	5.56 ± 1.50	28.03 ± 7.85	16
conventional together	4.14 ± 1.32	4.85 ± 1.52	**23.64 ± 7.55**	16
FD on-surface	4.45 ± 0.66	5.06 ± 0.85	25.40 ± 3.75	14
FD in-air	4.79 ± 0.73	5.48 ± 0.72	27.36 ± 4.20	19
FD together	4.55 ± 0.68	5.32 ± 0.78	26.00 ± 3.88	21
all on-surface	4.48 ± 0.86	5.12 ± 0.96	25.62 ± 4.92	16 (12 F, 4 C)
all in-air	4.95 ± 1.18	5.59 ± 1.17	28.30 ± 6.75	17 (13 F, 4 C)
all together	4.70 ± 1.10	5.45 ± 1.23	26.82 ± 6.30	17 (12 F, 6 C)

UPDRS V—Unified Parkinson's disease rating scale, part V: Modified Hoehn and Yahr staging score [17]; MAE—mean absolute error; RMSE—root mean squared error; EER—estimation error rate; F—FD-based features; C—conventional handwriting features; feat.—number of features important for the trained model (i.e., feature importance of the feature > 0.0); The feature importances, as well as the exact names of these features for models built to assess UPDRS V, are summarized in the text. In the case of PD duration, this data can be found in Table S1 provided in the Supplementary Material.

conventional on-surface (vertical normalized jerk (mean) of the repetitive word *lektorka*), conventional in-air (vertical velocity (mean) of the sentence), conventional together (vertical velocity (mean) of the sentence), FD on-surface (vertical velocity (std) $\alpha = 0.1$ of the sentence), FD in-air (vertical velocity (median) $\alpha = 0.3$ of the sentence), FD together (vertical velocity (std) $\alpha = 0.1$ of the sentence (on-surface; FI $= 0.50$), vertical velocity (median) $\alpha = 0.3$ of the sentence (in-air; FI $= 0.50$)), all on-surface (vertical velocity (std) $\alpha = 0.1$ of the sentence), all in-air (vertical velocity (median) $\alpha = 0.3$ of the sentence), and all together (vertical velocity (std) $\alpha = 0.1$ of the sentence (on-surface; FI $= 0.50$), vertical velocity (median) $\alpha = 0.3$ of the sentence (in-air; FI $= 0.50$)). With respect to PD duration, the lowest EER was achieved using conventional handwriting features computed for both on-surface as well as in-air movements (23.64 $\pm$ 7.55%).

III.4 Discussion

To the best of our knowledge, except for our pilot work [37], there are no prior studies which integrate FD into a handwriting parameterization for quantitative PD dysgraphia analysis. Therefore, the results published in this paper are exploratory in nature.

In comparison with the conventional kinematic features, FD-based ones correlate more significantly with the clinical characteristics (UPDRS V and PD duration). We observed especially strong correlations for handwriting tasks based on the periodic repetition of specific movements (Archimedean spiral; repetitive letter *l*, syllable *le*, or word *les*). Although the levels of significance based on the conventional handwriting parameters are lower, similar handwriting tasks are involved in the most significant results. We hypothesize that this is due to their ability to highlight or better quantify the cardinal motor symptoms of PD. For example, the most significant relationship between handwriting performance and PD duration was identified in acceleration extracted from the Archimedean spiral. Rigidity combined with tremor and/or bradykinesia makes a PD patient's handwriting/drawing less fluent (increased changes in velocity and higher acceleration). This is highlighted in a task such as the spiral, where the proper coordination of the fingers, wrist, and arm is required. Generally, the observed problems with coordination are in line with the work of Dounskaia et al. [11] and Teulings et al. [51]. To better illustrate these manifestations, Figure III.3 plots the velocity profiles of repetitive loops for a healthy control and a PD patient. As can be seen, the patient introduced more changes in velocity, and their drawing became much more non-fluent. To summarize these findings, FD features in combination with properly selected tasks provide a stronger relationship with the severity and progress of PD.

On the other hand, in terms of binary classification, the conventional parameters provided the best results. The classification performance is remarkable: ACC = 97.74%, SEN = 95.50%, and SPE = 100%. In fact, our results represent the highest classification accuracy that has ever been reported based on the PaHaW database (see Table III.1). We hypothesize that the improvement was caused by the inclusion of the state-of-the-art XGBoost algorithm into our machine learning pipelines. As already mentioned, the result is based on one in-air feature: median horizontal velocity of a sentence. In comparison with the HC cohort, the PD patients exhibited much lower values of this measure, i.e., while writing the sentence, the PD patients were not able to perform horizontal transitions (movement between neighboring letters or words) as quickly as the HC could. This finding is in line with the work

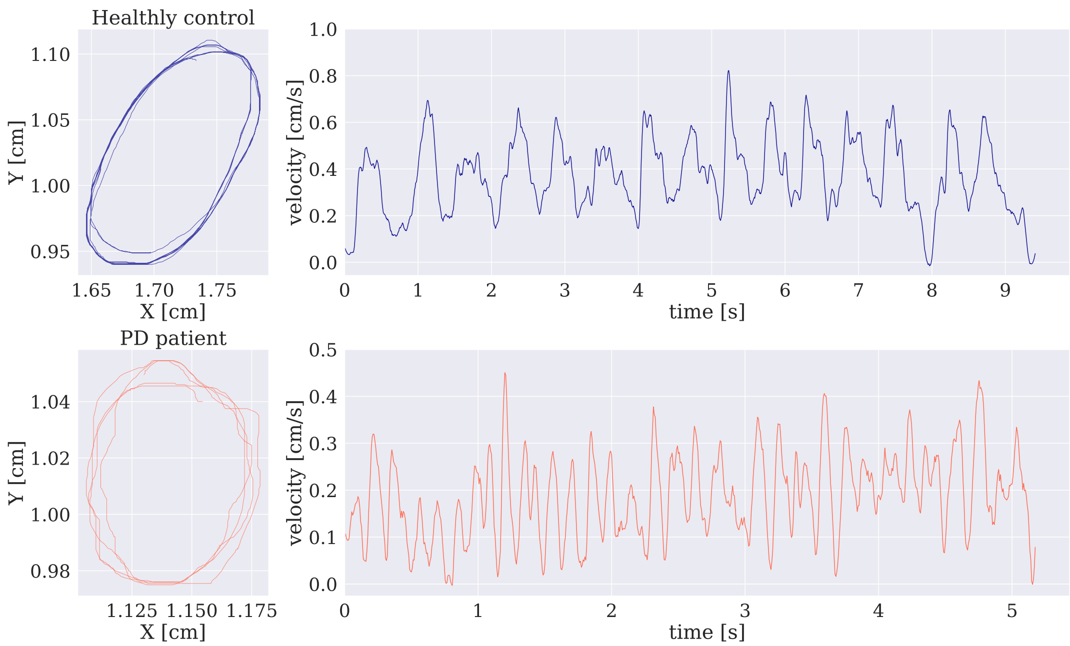

Fig. III.3: Handwriting samples of the repetitive loop task for HC and PD patients are on the left, and the resulting velocity profiles are on the right.

of Ma et al. [31], who observed that wrist extension stiffness in PD patients makes the handwriting in the horizontal direction more problematic. Therefore, scientists started to use the term *horizontal dysgraphia* [52]. Generally, vertical or horizontal dysgraphia may be considered a presymptomatic neurobehavioral biomarker of PD with possible significance in early PD diagnosis [52].

In [37], we proved that the FD features improved the accuracy of PD dysgraphia diagnosis in the Archimedean spiral drawing task by 10%. Contrary to our pilot results, in the frame of this work, these features did not lead to any improvements. After a deeper analysis, we found that this was caused by a combined task approach. Performance of the Archimedean spiral is a quasiparticle and continuous task with some repetitive patterns. It looks as though the FD features work especially well in these specific cases. Nevertheless, when combining these tasks with a complex handwriting task (such as a sentence), the measures quantifying in-air movement tend to be more discriminative (in our case, the median in-air horizontal velocity of a sentence). This brings us to the same conclusion that was given during the correlation analysis—the FD features advance the PD dysgraphia diagnosis only in some specific cases.

The best regression model, estimating the UPDRS V score with a 12.51% error, is based only on the standard deviation of on-surface vertical velocity ($\alpha = 0.1$) extracted from the sentence. This FD-based parameter was selected from the feature set combining all on-surface measures; therefore, we can confirm the positive influence of FC on the regression analysis performance. In fact, the FD features outperformed the conventional ones in all scenarios. To better understand this result, we plotted vertical velocity patterns of the sentence task for different orders of FD (see Figure III.4). We can observe a big difference between $\alpha = 0.1$ and the rest of the orders, including the full derivative. This large distance means that we are working with completely new information that is far from that contained in the full derivative. Although it is difficult to clinically interpret this information, it is clear that FC opens new possibilities for monitoring PD severity.

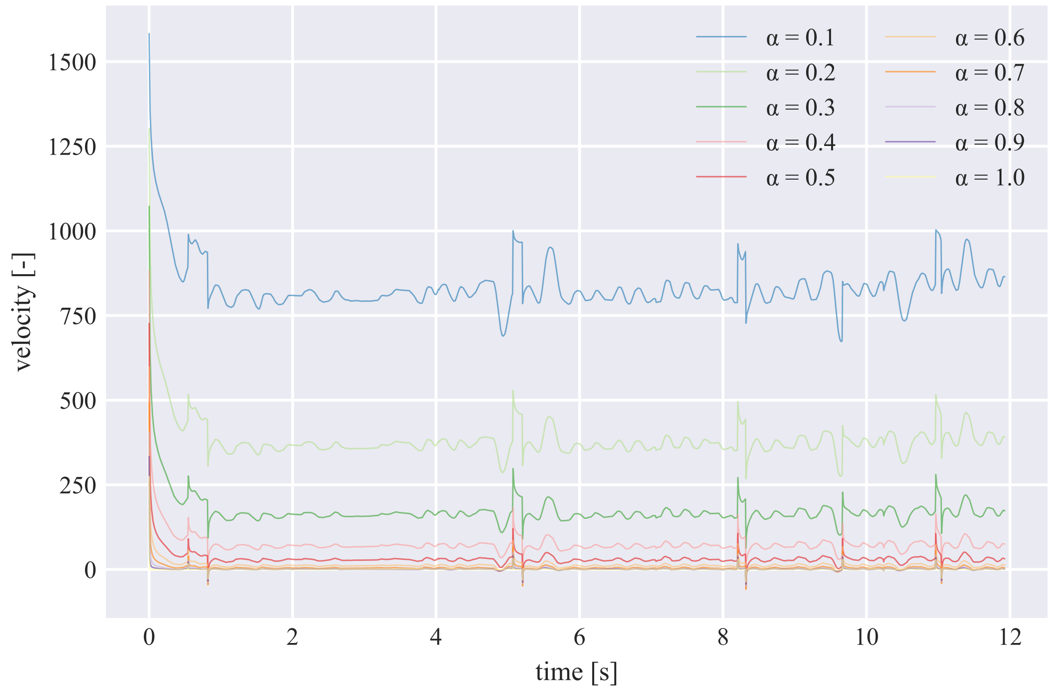

Fig. III.4: Vertical velocity patterns of the sentence task for different orders of fractional-order derivatives (FD).

Regarding the PD duration estimation results, the most successful model (EER = 23.46 %) consists of 16 conventional on-surface/in-air features (all features' importance values can be found in Supplementary Table S1). The most frequent feature with the highest feature importance is the jerk extracted from several handwriting tasks. This probably means that as PD progresses, handwriting becomes more jerky and irregular. Vertical velocity is the second most frequent feature involved in the models, which is probably linked with micrographia. Generally, in the case of PD duration estimation, the FD-based features did not yield any improvement.

In conclusion, the FD-based features are better for modeling PD severity (in terms of UPDRS V score estimation), but they do not lead to an improvement in PD duration modeling. The progress of PD is nonlinear and very individual. This means that patients with the same PD duration can be in different stages of the disease. This fact supports our results: the estimation error of PD duration was generally much worse than the estimation error of the UPDRS V score. Since PD duration estimation is a difficult task with poor results, fine improvements based on FD parameters play no role.

III.5 Conclusions

This study deals with advanced approaches to PD dysgraphia diagnosis and monitoring based on FC integrated with online handwriting/drawing parameterization. To the best of our knowledge, it is the first work that performs a complex investigation into the possibilities for FC in online handwriting processing and proposes new advances in kinematic analyses based on FD. Although the conventional features provided better and very high classification accuracy, which is at the top of the state-of-the-art analyses based on the PaHaW database (ACC = 97.74%, SEN = 95.50%, and SPE = 100%), the newly designed parameters were proven to work better for specific tasks (continuous and/or repetitive, such as the Archimedean spiral) and for specific applications, i.e., PD severity estimation (EER = 12.51%). However, our results need to be confirmed by subsequent scientific research.

This study has several limitations and suggestions for further improvements. Since the dataset is small, to be able to generalize the results, bigger databases should be involved. On the other hand, it is common to have such small numbers of PD patients and HC samples in PD dysgraphia analysis, e.g., see our review in Table III.1. Next, we considered only the kinematic measures. To better evaluate the discrimination power of the FD features and better evaluate their ability to estimate PD severity or progress, other feature types, such as temporal, spatial, and dynamic, should be included in future comparisons. Finally, the FD-based parameters could be further explored. For instance, we can consider other approximations (e.g., Caputo) or employ FC for other measures (e.g., entropies).

Supplementary Materials

The following are available online at mdpi.com/2076-3417/8/12/2566/s1, Table S1: Feature relevance from multivariate regression (modeling PD duration).

Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ACC	accuracy
ADA	AdaBoost
ANN	artificial neural network
ANOVA	analysis of variance
AUC	area under the ROC curve
CNN	convolutional neural network
EMD	empirical mode decomposition
EER	estimated error rate
FN	false negatives
FP	false positives
FC	fractional calculus
FD	fractional-order derivative
FI	feature importance
K-NN	K-nearest neighbors
LED	L-dopa equivalent daily dose
LDA	linear discriminant analysis
MCC	Matthew's correlation coefficient
max	maximum
MAE	mean absolute error
NB	naïve Bayes classifier
OPF	optimum path forest
PD	Parkinson's disease
RF	random forests
RMSE	root mean squared error
SEN	sensitivity
r_p	Pearson's correlation coefficient
r_s	Spearman's correlation coefficient
SPE	specificity
std	standard deviation
TN	true negatives
TP	true positives
SVM	support vector machine

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IV Advanced Analysis of Online Handwriting in a Multilingual Cohort of Patients with Parkinson's Disease

Outline

Bibliographic Information

J. Mucha, J. Mekyska, M. Faundez-Zanuy, P. Sanz-Cartagena, Z. Galaz, V. Zvoncak, T. Kiska, Z. Smekal, K. Lopez-de-Ipina and I. Rektorova. Advanced Analysis of Online Handwriting in a Multilingual Cohort of Patients with Parkinson's Disease. In *1st International Conference on Advances in Signal Processing and Artificial Intelligence (ASPAI' 2019)*, pages 144-147. IFSA, 2019.

Author's Contribution

The author proposed the topic of the paper, surveyed related works, designed the methodology, performed analysis, validated and co-investigated the results. He also prepared the original draft and final version of the manuscript.

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Abstract

The majority of Parkinson's disease (PD) patients suffer from handwriting abnormalities commonly called as Parkinsonic dysgraphia. Several approaches of PD dysgraphia analysis exist, e.g. based on online handwriting processing. However, a small and unilingual cohort of PD patients is often an issue in quantitative PD dysgraphia analysis studies. Therefore, in this work, we aim to perform a discrimination analysis in a multilingual cohort of 73 PD patients and 48 healthy controls (Spanish and Czech). For this purpose, we extracted advanced handwriting features based on fractional order derivatives (FD). Discrimination power of the advanced FD-based features was evaluated by Mann-Whitney U test and random forests classifier. We reached 82 % classification accuracy (86 % sensitivity, 77 % specificity) in the multilingual cohort. In addition, we observed high discrimination power of the FD-based parameters and proofed the high impact of online handwriting processing in cross-cultural PD dysgraphia analysis studies.

Acknowledgment

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IV.1 Introduction

Parkinson's disease (PD), as the second most frequent neurodegenerative disorder, affects approximately 1.5 % of the world population aged over 65 years [1]. A rapid degeneration of dopaminergic cells in substancia nigra pars compacta emerged as the most important biological finding accompanying the disease [5]. Considering the cardinal motor symptoms of PD (tremor in rest, bradykinesia and rigidity) in conjunction with cognitive, perceptual and motor requirements of handwriting, the disrupted handwriting of PD patients may be used as a significant biomarker for PD diagnosis [3]. The most commonly observed handwriting abnormality in PD patients is micrographia (progressive decrease of letters amplitude) [10], which may be noticed even before the onset of PD motor symptoms in approximately 5 % of PD patients.

Nowadays, by utilizing digitizing tablets, which brings an ability to acquire x and y position with temporal information, we have the opportunity to process online handwriting signals. Therefore, we are not limited to analyze the spatial features only, but we are able to quantify more manifestations of PD appearing in patients handwriting data (temporal, kinematic or dynamic), generally named as PD dysgraphia [8].

The impact of quantitative PD dysgraphia analysis employing several handwriting or drawing tasks (e. g. characters, loops, sentences, figures) has been explored in [13, 14, 4, 7]. Researchers usually use kinematic, temporal, spatial or dynamic handwriting features in PD dysgraphia analysis. However, more advanced parameters (based on entropy, energy operators or empirical mode decomposition) have been reported too. PD dysgraphia classification accuracies reported by recent works vary in the range of 85 and 97 %. In our previous works [13, 11, 12], we proposed and evaluated a new advanced approach of kinematic analysis based on fractional order derivatives (FD). Using this approach, we were able to identify PD with almost 90 % accuracy employing only 5 basic kinematic features.

The most common issue in PD differential analysis (cause by complicated and time-consuming patient examination process), which researchers are encountering with, is a small and unilingual cohort of patients. This may result into poor generalization. Especially, the size of examining dataset has a significant influence on results reliability. The smallest the dataset is, the more misleading results may be. Therefore, in this study, we aimed to analyze a multilingual cohort involving two PD handwriting databases (Czech and Spanish) in order to train a more robust classification model. To our best knowledge, this is the first study considering multilingual cohort in PD dysgraphia analysis.

IV.2 Datasets and Methodology

IV.2.1 Dataset

For the purpose of this study, we used two PD handwriting databases. The Czech (PaHaW [4]) database consists of 37 PD patients and 38 healthy controls (HC). It includes 9 different handwriting tasks (Archimedean spiral, repetitive loops, repetitive letter l, syllable, words and sentence). The Spanish database (recorded in Mataró Hospital, Spain) consists of 36 PD patients and 10 HC. It includes 2 handwriting tasks (repetitive and continuously written letter l and sentence). Demographic and clinical data of both cohorts can be found in Table IV.1. All patients were examined on their regular dopaminergic medication approximately 1 hour after the L-dopa dose. All participants were right-handed, and all participants signed an informed consent form approved by the local ethics committees.

Table IV.1: Demographic and clinical data of all participants

Cohort	Number	Age [y]	PD dur [y]
Parkinson's disease patients			
Czech	37	69.21 ± 11.10	8.70 ± 4.82
Spanish	36	68.25 ± 10.46	6.10 ± 3.78
Healthy controls			
Czech	38	62.50 ± 11.70	-
Spanish	10	57.50 ± 6.36	-

y – years; PD dur – PD duartion.

For the purpose of this study, sentence handwriting task was selected from the databases. Even the tasks are different due to language, we hypothese that pathological characteristics in the handwritten signals will be similar. Sentences in their original language and with resulting English translations are listed below:

- Czech: “Tramvaj dnes už nepojede.”
  English: The tram will no longer go today.
- Spanish “La casa de Barcelona es preciósa.”
  English: The house in Barcelona is beautiful.

Samples of PD patients' sentences can be found in Figure IV.1. In Figure IV.2, descriptive statistics of both datasets are visualized. Handwriting data were acquired using a digitizing tablet Wacom Intuos 4M (both datasets). Following time sequences were sampled with frequency fs = 150 Hz: x and y coordinates (x[t], y[t]); time-stamp (t); in-air/on-surface status (b[t]); pressure (p[t]); azimuth (az[t]); and tilt (al[t]).

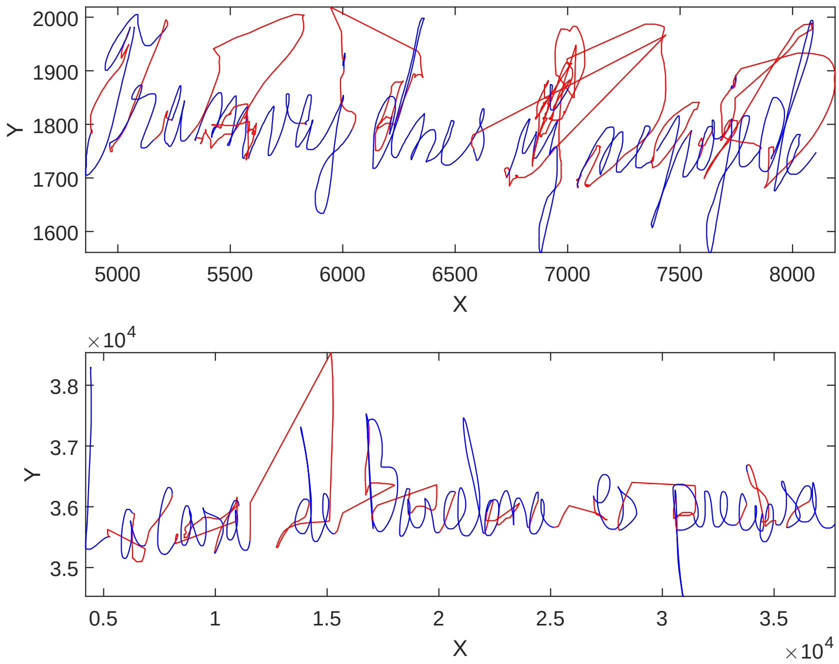

Fig. IV.1: PD patient's sentences examples. Czech sentence in the upper part and Spanish in the bottom part of the figure. On-surface (blue) and in-air (red) movement are visualized.

IV.2.2 Methodology

Firstly, each handwritten signal was split into on-surface and in-air movements [18] (see FigureIV.1). Next, basic kinematic features such as velocity, acceleration and jerk were extracted. Instead of conventional differential derivative, we utilized FD as an advanced approach of kinematic features calculation. For this purpose, the Grünwald-Letnikov approximation was used [16] [6]. The advantage of FD is based on their extensive range of settings and several approaches of approximation. Moreover, we also applied FD on pen pressure, azimuth and tilt signals. All features were extracted for different values of α (order of FD). In the frame of this work, a range from 0.1 to 1.0 with a step of 0.1 was used. Finally, statistical properties of the features were described by: mean, median, standard deviation (std), and maximum (max). Altogether, 1188 handwriting features were extracted for each dataset.

We were considering 3 following feature sets: Czech, Spanish and multilingual (mixed – 73 PD, 48 HC). In order to identify features that discriminate HC and PD we employed the Mann-Whitney U test. The significance level was set to $p < 0.001$.

Next, to evaluate the discrimination power of handwriting features, we performed multivariate classification analysis based on random forests (RF) [2]. In order to reduce the number of handwriting features entering into the classification analysis,

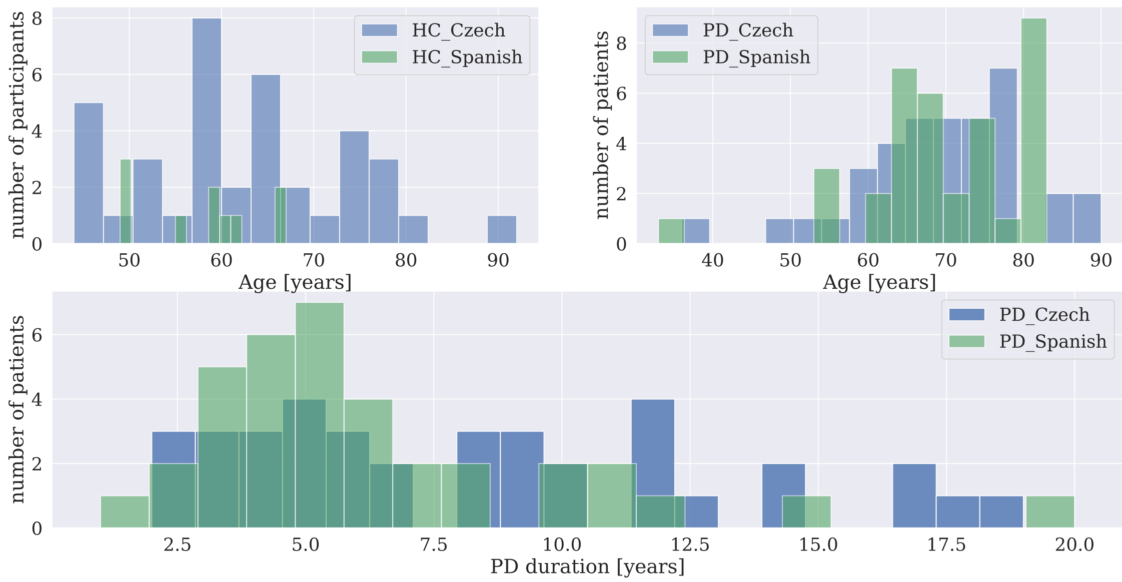

Fig. IV.2: Descriptive statistics of examined datasets. In the top left part of the figure, the HC age distribution is visualized. The PD age distribution is in the top right part and in the bottom part, the distribution of PD duration is shown.

we designed fast and efficient 2-stage feature selection. Firstly, each feature set was reduced by minimum redundancy maximum relevance [15] (mRMR) feature selection algorithm to 50 best features. Secondly, to obtain the most appropriate combination of the features, the sequential floating forward selection [17] (SFFS) algorithm was employed. To achieve the most accurate results for each dataset, we used different types of model validation techniques. In the case of Czech and Spanish feature sets we used leave-one-out cross-validation (due to small sample size). For the multilingual feature set, 10-fold cross-validation with 20 repetition was used. Classification performance was evaluated by the Matthew's correlation coefficient [9] (MCC), classification accuracy (ACC), sensitivity (SEN) and specificity (SPE).

IV.3 Results

The results of the Mann-Whitney U test can be found in the upper part of Table IV.2. Three most discriminative features which passed through the test are reported for each feature set. Features are sorted by significance level p, while all reported features obtained $p < 0.0001$. The most discriminative feature from the Spanish feature set is velocity (on-surface). In the case of Czech and multilingual feature set, it is its vertical variant, which is probably linked with the vertical micrographia [19]. As can be noticed, the results of the Czech and multilingual feature sets are quite similar, in comparison with Spanish one. This is probably caused by the size of the

Spanish HC cohort (10 participants).

Next, the results of the multivariate classification analysis can be found in the bottom part of Table IV.2. The highest classification performance was obtained in the Spanish feature set (ACC = 95.65 %), nevertheless, due to the imbalanced cohort (36 PD patients and 10 HC), these results may be misleading. Number of HC in the Spanish database is 3.6 times lower than number of PD patients. By mixing the Spanish and Czech (well balanced) databases we have reduced the imbalance of the Spanish one (PD $\approx$ .5 x HC). Also, the distribution of PD duration for the Czech cohort is more uniform (see Figure IV.2). In the Spanish cohort, patients with shorter disease duration (less than 6 years) outweigh, however the distribution of PD patient's age is quite similar for both cohorts. Thus, by combining the datasets, we also improved non-uniformity of the final cohort. Although the accuracy of the multilingual feature set is the lowest one (82.29 %), credibility of the results may be considered as higher in comparison to the Spanish feature set.

Table IV.2: Results of Mann-Whitney U test and classification analysis

Mann-Withney U test			
Feature set	Feature Name	α	p
Spanish	velocity (on-surface) (median)	0.1	0.000069
	velocity (on-surface)(median)	0.2	0.000069
	velocity (in-air) (mean)	0.1	0.000077
Czech	vertical velocity (on-surface) (mean)	0.2	0.000012
	vertical velocity (on-surface) (mean)	0.2	0.000014
	vertical velocity (on-surface) (median)	0.4	0.000014
Multilingual	vertical velocity (on-surface) (mean)	0.1	0.000001
	vertical velocity (on-surface) (median)	0.4	0.000001
	vertical velocity (on-surface) (median)	0.3	0.000001

Multivariate classification analysis					
Feature set	N	MCC	ACC [%]	SEN [%]	SPE [%]
Spanish	2	0.87	95.65	97.22	90
Czech	9	0.71	85.33	89.19	81.58
Multilingual	8	0.63	82.29	85.99	77.22

α – order of FD; p – significance level; N – number of features.

IV.4 Conclusion

This study deals with the advanced analysis of PD dysgraphia in a multilingual cohort. First of all, since the most significant features identified in the Mann-Whitney U test and features selected by the SFFS have a non-integer value of the FD order, we suppose that the FD based parameters play significant role in PD dysgraphia quantification. Next, we achieved more than 80 % classification accuracy in all scenarios, which suggests the high impact of online handwriting processing in cross-cultural clinical studies focused on PD dysgraphia diagnosis. This study has several limitations and suggestions for further research. Firstly, the Spanish dataset is not balanced (PD/HC, PD duration). In addition, the overall sample size is not big. On the other hand, to the best of our knowledge, it is the first and therefore the biggest multilingual online handwriting PD dataset, that has ever been analyzed. Finally, the FD-based features may be more explored and extended (e.g. by Caputo approximation approach). To sum it up, this study has a pilot character and further research should be done to be able to generalize the results.

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V Analysis of Parkinson's Disease Dysgraphia Based on Optimized Fractional Order Derivatives Features

Outline

Bibliographic Information

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Author's Contribution

The author surveyed related works, proposed a optimization, designed and performed the analysis, and wrote a significant part of the manuscript. He was also working on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder with prevalence rate estimated to 1.5 % for people age over 65 years. The majority of PD patients is associated with handwriting abnormalities called PD dysgraphia, which is linked with rigidity and bradykinesia of muscles involved in the handwriting process. One of the effective approaches of quantitative PD dysgraphia analysis is based on online handwriting processing. In the frame of this study we aim to deeply evaluate and optimize advanced PD handwriting quantification based on fractional order derivatives (FD). For this purpose, we used 37 PD patients and 38 healthy controls from the PaHaW (PD handwriting database). The FD based features were employed in classification and regression analysis (using gradient boosted trees), and evaluated in terms of their discrimination power and abilities to assess severity of PD. The results suggest that the most discriminative and descriptive information provide FD based features extracted from a repetitive loop task or a sentence copy task (maximum sensitivity/specificity = 76 %, error in severity assessment = 14 %, error in PD duration estimation = 22 %). Next, we identified two optimal ranges for the order of fractional derivative, $\alpha = 0.05-0.45$ and $\alpha = 0.65-0.80$. Finally, we observed that inclusion of pressure, azimuth, and tilt together with kinematic features into mathematical modeling has no influence (positive or negative) on classification performance, however, there was a notable improvement in the estimation of PD duration.

Acknowledgment

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V.1 Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder affecting approximately 1.5 % of the world population aged over 65 years [1]. The risk of being affected by PD increases with age. Therefore, as populations age, the incidence rate is expected to be doubled in the next 15 years [8]. The exact pathophysiological cause of PD has not yet been discovered, though a rapid degeneration of dopaminergic cells in the substantia nigra pars compacta is the most significant biological finding linked with PD. Tremor at rest, rigidity, bradykinesia and postural instability are considered as the primary motor symptoms of PD [10]. Non-motor symptoms such as cognitive impairment, sleep disturbances, depression, etc. may also arise [9, 16]. Moreover, PD patients usually develop additional axial motor symptoms, e.g. hypokinetic dysarthria, dysphagia, and gait freezing [16].

Considering the primary motor symptoms of PD to be in line with cognitive, perceptual and motor requirements of handwriting, the disrupted handwriting of PD patients may be used as a significant biomarker in PD diagnosis [3]. Especially, by detecting micrographia (progressive decrease of letter's amplitude or width), which is the most commonly observed handwriting abnormality in PD patients [14]. Nevertheless, some PD patients never develop micrographia, but they still exhibit some other handwriting disabilities. Due to this complexity, Letanneux et al. [12] started to use the term PD dysgraphia. To be able to effectively quantify manifestations of PD in handwriting, more advanced approaches were introduced [24, 6]. They are based on digitizing tablets that are able to acquire x and y trajectories along with temporal information (this kind of signal is called online handwriting). Therefore, we are not limited to analyze the spatial features only, but we can process temporal, kinematic or dynamic characteristics.

Researchers have been exploring the influence of many handwriting/drawing tasks in PD dysgraphia analysis, from the simplest ones (loops, circles, lines, Archimedean spiral, etc.) to more complex (words, sentences, drawings, etc.) [6, 4, 5, 21, 19, 18]. The importance of kinematic features was confirmed by most of the recent works, however, temporal, spatial, dynamic or other more advanced features play their significant role as well. For instance, Drotar et al. [6, 4, 5] achieved PD classification accuracy up to 89 % using a combination of kinematic, pressure, energy or empirical mode decomposition (EMD) features. Average accuracy of 91 % was achieved by Kotsavasilogloua et al. [11] using kinematic and entropy based features extracted from simple horizontal lines. Some other works reported even higher classification accuracies ($\approx$97 %) [13, 23], but based on a very small dataset. Moetesum et al. [17] published a promising advanced approach by applying convolutional neural networks (CNN) on handwriting data transformed into the offline mode, which resulted in 89 % accuracy. Next, Taleb et al. [24] reported up to 94 % accuracy of PD severity prediction using kinematic and pressure features in combination with adaptive synthetic sampling approach (ADASYN) for model training. Finally, in our recent works [19, 18, 20] we introduced and evaluated a new advanced approach of PD dysgraphia analysis exploiting a fractional order derivative (FD) as a substitution of conventional differential derivative during basic kinematic feature extraction (i.e. velocity, acceleration, and jerk parameters). We achieved up to 90 % classification accuracy employing only 5 FD-based kinematic parameters in these works. Nevertheless, in comparison to conventional parameters, the newly proposed FD-based features yielded better performance only in specific tasks (continuous and/or repetitive movement) and in specific applications such as PD severity estimation.

Therefore, the main objective of this study is to extend our previous findings and perform a deeper and more sensitive analysis of FD-based features, especially in terms of their discrimination power and descriptive abilities. More specifically, we aim to:

- explore the utilization of FD in the other dimensions of online handwriting (i.e. pressure, azimuth, and tilt),
- identify an optimal combination of handwriting/drawing tasks and the FD-based features in terms of discrimination power and descriptive abilities,
- identify an optimal range of FD order α for classification and regression analysis.

The rest of this paper is organized as follows. Section V.2 describes the used dataset and methodology. Results are summarized in Section V.3. In Section V.4 the discussion related to the results can be found and the conclusions are drawn in Section V.5.

V.2 Dataset and Methodology

V.2.1 Dataset

For the purpose of this work, we used the Parkinson's disease handwriting database (PaHaW) [4]. The database consists of several handwriting or drawing tasks acquired in 37 PD patients and 38 age- and gender-matched healthy controls (HC). Demographic and clinical data of the participants can be found in Table V.1. The participants were enrolled at the First Department of Neurology, St. Anne's University Hospital in Brno, Czech Republic. All participants reported Czech language as their native language and they were right-handed. The patients completed their tasks approximately 1 hour after their regular dopaminergic medication (L-dopa).

All participants signed an informed consent form approved by the local ethics committee.

Table V.1: Demographic and clinical data of the enrolled participants.

Gender	N	Age [y]	PD dur [y]	UPDRS V	LED [mg/day]
Parkinson's disease patients					
Females	18	71.23 ± 8.03	9.55 ± 5.29	2.17 ± 0.84	1124.03 ± 535.84
Males	19	67.52 ± 13.15	7.26 ± 4.12	2.37 ± 0.86	1724.12 ± 733.03
All	37	69.32 ± 10.97	8.38 ± 4.80	2.27 ± 0.85	1432.19 ± 704.78
Healthy controls					
Females	18	61.44 ± 9.89	-	-	-
Males	20	63.30 ± 12.79	-	-	-
All	38	62.42 ± 11.39	-	-	-

[1] N – number of subjects; y – years; PD dur – PD duration; UPDRS V – Unified Parkinson's disease rating scale, part V: Modified Hoehn & Yahr staging score [7]; LED – L-dopa equivalent daily dose.

V.2.2 Data Acquisition

The PaHaW database [4] includes multiple handwriting tasks, namely: Archimedean spiral; repetitive loops; letter *l*; syllable *le*; Czech words *les*, *lektorka*, *porovnat*, and *nepopadnout*; Czech sentence *Tramvaj dnes už nepojede.* During handwriting tasks performance, the participants were rested and seated in a comfortable position with a possibility to look at a pre-filled template. In case of some mistakes, they were allowed to repeat the task. A digitizing tablet (Wacom Intuos 4M) was overlaid with an empty paper and the participants wrote on that using the Wacom Inking pen. Online handwriting signals were recorded with $f_{\mathrm{s}} = 150$ Hz sampling rate. The following time sequences were acquired: x and y coordinates – $x[t]$, $y[t]$; time-stamp – t; on-surface (i.e. on paper movement) and in-air (i.e. movement up to 1.5 cm above the paper) status – $b[t]$; pressure – $p[t]$; azimuth $az[t]$; and tilt $al[t]$.

V.2.3 Fractional Derivative

We discovered the potential of FD-based kinematic features in PD dysgraphia analysis in our previous works [19, 18, 20]. By substitution of the conventional differential derivative during feature calculation, we have developed a new advanced approach of handwriting parametrization. Generally, FDs can have wide range of settings and several approaches of approximation (e.g. Caputo, Grünwald-Letnikov) [22].

In this work, we utilized the Grünwald-Letnikov approximation implemented by Jonathan Hadida. A direct definition of FD $D^\alpha y(t)$ is based on finite differences of an equidistant grid in $[0, \tau]$ assuming that the function $y(\tau)$ satisfies certain smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid [22]

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{V.1}$$

with

$$\tau_{k+1} - \tau_k = h \tag{V.2}$$

and using the notation of the finite differences

$$\frac{1}{h^\alpha}\Delta_h^\alpha y(t) = \frac{1}{h^\alpha}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^\alpha y(\tau_{n+1-v})\right), \tag{V.3}$$

where

$$c_v^\alpha = (-1)^{v-1}\tbinom{\alpha}{v}. \tag{V.4}$$

The Grünwald-Letnikov implementation is defined as:

$$D^\alpha y(t) = \lim_{h \to 0} \frac{1}{h^\alpha}\Delta_h^\alpha y(t), \tag{V.5}$$

where $D^\alpha y(t)$ denotes a derivative with order α of function $y(t)$, and h represents sampling lattice.

V.2.4 Handwriting Features

The first set of parameters consists of conventional kinematic features extracted from all tasks of the PaHaW database for both on-surface and in-air movement. It means we calculated: *velocity* (rate at which a position of pen changes with time [mm/s]), *acceleration* (rate at which the velocity of pen changes with time [mm/s^2]), *jerk* (rate at which the acceleration of pen changes with time [mm/s^3]), and their horizontal and vertical variants [4, 15]. Next, we calculated the kinematic features based on FD. Moreover, to further extend and improve our previous research, FD was also similarly applied to pressure, azimuth and tilt.

In the first step, the FD-based features were calculated for different values of α in range from 0.1 to 1.0 with the step of 0.1. Next, the most discriminative handwriting tasks were selected and deeper analysed with a finer step of α (0.01). This selection was made in order to reduce computational cost of the analysis. Statistical properties of all extracted handwriting features were expressed using mean, median, standard deviation (std), and maximum (max).

V.2.5 Statistical Analysis

To evaluate the discriminative power of the handwriting features, a multivariate binary classification analysis based on the state-of-the-art Gradient Boosted Trees (10-fold cross-validation with 50 repetitions) was employed. More specifically, the famous XGBoost algorithm [2] was used in light of its ability to achieve good performance on a small dataset. Classification performance was evaluated by the Matthew's correlation coefficient (MCC), classification accuracy (ACC), sensitivity (SEN), and specificity (SPE). Next, in order to evaluate the power of handwriting features to estimate values of PD duration and UPDRS V, regression analysis was performed. The same boosting tree algorithm (XGBoost) with the same supervised learning setup was used. Regression performance was evaluated by mean absolute error (MAE), root mean square error (RMSE), and estimation error rate (EER).

V.3 Results

The results of classification and regression analysis for the FD-based handwriting features extracted from all tasks can be found in Table V.2. Selection of the most discriminative/descriptive handwriting tasks for the consequent optimization of FD was performed based on feature importances of trained models (feature importance quantifies the relative importance of the feature in an ensemble of the trained XG-Boost model [2]). Distribution of particular tasks and derived features for all classification/regression scenarios can be found in Figure V.1. Results of the classification/regression analysis after the fine tuning of FD are reported in Table V.3. Finally, distributions of the FD order α among the fine-tuned parameters are visualized in Figure V.2.

V.4 Discussion

Firstly, we performed the analysis using all tasks of the PaHaW database utilizing features calculated for α from 0.1 to 1.0 with step 0.1 (10 FD-based features for one handwriting parameter). As can be seen in the upper part of Table V.2, ACC (80.60 %) corresponds with our previous results (81.43 %) [19], while SEN and SPE were improved by approximately 10 %. Number of features involved in the trained model is 18, and as can be seen in Figure V.1 (bottom part of column a), besides the kinematic features the pressure and azimuth parameters are also modeled. Based on the distribution reported in the upper part of column a) (see Figure V.1), it is noticeable that the highest discriminative power provide repetitive loops. Regarding the results of regression analysis, the most suitable task for further optimization of

Table V.2: Results of classification and regression analysis based on all tasks

Classification				
MCC	ACC [%]	SEN [%]	SPE [%]	Feat
0.62 ± 0.14	80.60 ± 9.87	79.41 ± 14.52	80.56 ± 7.25	18
Regression				
Scale	EER [%]	MAE	RMSE	Feat
UPDRS V	12.98 ± 7.01	0.55 ± 0.29	0.66 ± 0.42	3
PD duration	25.23 ± 3.65	4.42 ± 0.64	5.33 ± 0.89	30

[1] MCC – Matthew's correlation coefficient; ACC – accuracy; SEN – sensitivity; SPE – specificity; Feat – number of features important for the trained model; MAE – mean absolute error; RMSE – root mean squared error; EER – estimation error rate; UPDRS V – Unified Parkinson's disease rating scale, part V: Modified Hoehn & Yahr staging score [7].

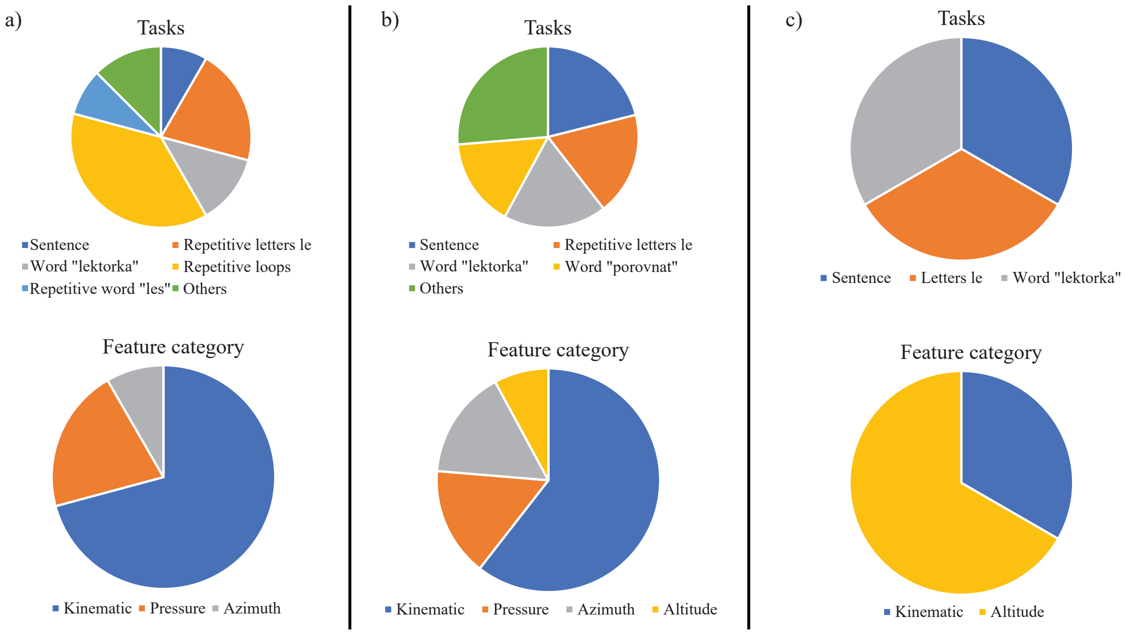

Fig. V.1: Distribution of particular tasks and derived features in the trained XG-Boost models: a) classification analysis; b) regression analysis (PD duration); c) regression analysis (UPDRS V).

Table V.3: Results of classification and regression analysis for selected tasks

Classification					
Task	MCC	ACC [%]	SEN [%]	SPE [%]	Feat
Sentence	0.34 ± 0.18	66.67 ± 12.45	65.79 ± 18.12	65.79 ± 21.58	21
Rep. loops	0.52 ± 0.11	76.00 ± 11.98	75.68 ± 12.36	76.32 ± 19.54	11
Regression					
Task	Scale	EER [%]	MAE	RMSE	Feat
Sentence	UPDRS V	14.67 ± 7.44	0.63 ± 0.32	0.78 ± 0.40	1
Rep. loops	UPDRS V	13.94 ± 7.61	0.61 ± 0.33	0.75 ± 0.41	2
Sentence	PD duration	23.73 ± 10.67	4.05 ± 1.82	4.62 ± 1.83	33
Rep. loops	PD duration	21.97 ± 8.97	3.75 ± 1.53	4.36 ± 1.60	39

[1] MCC – Matthew's correlation coefficient; ACC – accuracy; SEN – sensitivity; SPE – specificity; Feat – number of features important for the trained model; MAE – mean absolute error; RMSE – root mean squared error; EER – estimation error rate; UPDRS V – Unified Parkinson's disease rating scale, part V: Modified Hoehn & Yahr staging score [7].

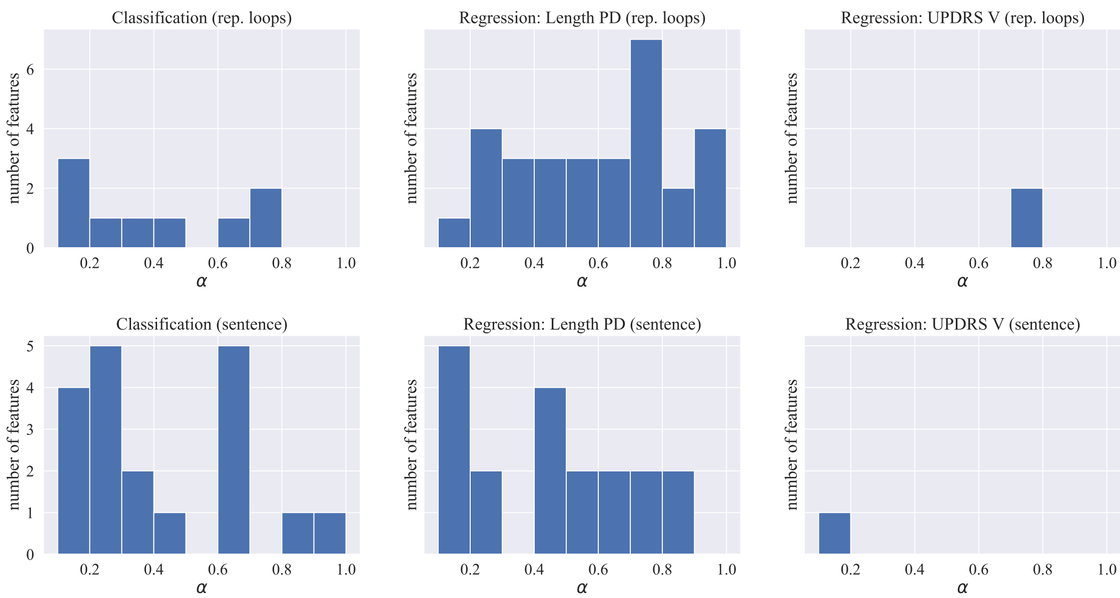

Fig. V.2: Distributions of FD order α among the fine-tuned parameters.

the FD-based features is the sentence (see the upper part of column b) and c) in Figure V.1). In comparison with our previous results [19], the estimation error of PD duration differs minimally, however, the resulted models include parameters coming from all feature categories. In the case of UPDRS V, the value of EER is similar again, but in this case, most of the features are tilt-based instead of kinematic-based. Considering the facts mentioned above, we can conclude that utilizing FD analysis of pressure, azimuth and tilt does not have any noticeable effect on model's performance.

Secondly, we performed the optimization of FD-based features extracted from the repetitive loops and sentence. We re-calculated these features for α from 0.01 to 1.00 with 0.01 step (100 FD-based features for one time sequence) in order to identify the optimal values of α. As can be seen in the upper part of Table V.3, ACC for both tasks is lower in comparison with the all task classification. It is the consequence of using just a single task for classification, and it corresponds with previous works [6, 4, 19, 20]. Nevertheless, we have to point out that the main objective of this step is not to increase the classification accuracy but to identify the optimal values of α. It is visible from the first column of Figure V.2 that the optimal α for PD classification is in ranges from 0.05 to 0.35 and 0.60 to 0.75. Regarding the results of regression analysis, in the case of UPDRS V estimation, EER is slightly worse in comparison with the first step. In the case of PD duration estimation, EER is slightly better (by $2-3.5\,\%$) than in the first step and also in comparison with our previous work [19] it was improved by $5\,\%$. These results are probably caused by the usage of fine-tuned FD-based features. From the middle and last column in Figure V.2, we may conclude that the optimal value of α for PD severity assessment and duration estimation is in ranges from 0.05 to 0.45 and from 0.65 to 0.80. By inter-sectioning optimal α ranges of classification and regression analysis, we created a final optimal range of α from 0.05 to 0.45 and from 0.60 to 0.80, that is recommended to be used in the field of PD dysgraphia analysis.

V.5 Conclusion

Based on the results we can conclude that applying FD on pressure, azimuth and tilt profiles has no influence (negative or positive) on classification performance. However, there was a notable improvement in the estimation of PD duration by $19\,\%$. Next, in the field of PD dysgraphia analysis, we identified the optimal values of the FD order, which should be in the range from 0.05 to 0.45 or from 0.60 to 0.80. Identification of these ranges enables significant reduction of computational cost (by approximately $50\,\%$), because researchers do not have to explore the full range of possible values of the FD order during quantitative analysis of PD dysgraphia.

This study has several limitations and possible parts, that could be further improved/explored. Since the processed dataset is small, further studies on this topic should be held in order to generalize the results. Next, the FD order could be further tuned for horizontal and vertical movement separately. And finally, some other approximations of FD (e.g. Caputo's) can further improve classification or regression performance.

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VI Fractional Order Derivatives Evaluation in Computerized Assessment of Handwriting Difficulties in School-aged Children

Outline

Bibliographic Information

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Author's Contribution

The author proposed a new method usage, co-designed and performed the analysis, and wrote a methodology part of the manuscript. He was also working on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

Handwriting difficulties (HD) affects some of the school-aged children and its current prevalence rate is between 5–34 %. Children at primary schools have to face rising cognitive demands that the handwriting represents, and some of them are not able to do so. As a result, they tend to make mistakes and their written product is dysfluent and has poor legibility. HD can also lead them to lower self-esteem, learning difficulties and ultimately to less academic achievements. For this reason occupational therapists are trying to identify HD through examination as early as possible. We extracted online handwriting signals of children using digitizing tablets. Handwriting Proficiency Screening Questionnaire for Children (HPSQ–C) was used to score severity of HD in children's written product. To advance current computerized analysis of online handwriting, we employed fractional order derivative features (FD) together with conventional measures. We selected significant features for HD identification and utilized correlation analysis together with Mann-Whitney U-test to evaluate their discriminative power. We can conclude that FD-based features bring benefits of more robust quantification of in-air movements as opposed to the conventionally used ones. Finally, we have shown that utilization of FD can be beneficial for computerized assessment of HD but should be further optimized and evaluated with advanced statistical or machine learning methods.

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VI.1 Introduction

In childhood, mastering legible handwriting is an important skill [1]. During this life period, a child has to develop adequate cognitive and motor abilities, such as fine motor control, stroke formation, thumb-to-finger sequencing, visual processing, formulation of an idea, planing a syntax of a sentence, achieving orthographic-motor integration to produce text, and evaluation of the outcome [26]. In fact, many children have problems to withstand rising cognitive demands that the handwriting represents, and are not able to comprehend simultaneous tasks such as grammar, spelling, composition [5], etc. As a result, their written product is dysfluent, it has poor legibility, and the in-air time (time spent above the writing surface) is generally longer [28]. Moreover, these children spend too much effort during handwriting, which leads to low dexterity [29] as well as the lack of fine motor control [8]. This phenomenon is commonly referred to as *handwriting difficulties* (HD) and its prevalence range between 5–34 % [4].

At present, occupational therapists examine HD based on the following criteria [12]: legibility and speed of writing, performance time, quality of letter formation, alignment, number of errors, spacing and sizing of letters, etc. Although the clinical assessment of HD provides valuable information about handwriting, it is still limited to a visual inspection of the written product, which does not provide complete information about the process itself. Besides, such an assessment is also dependent on the examiner's experience, level of expertise, physical and emotional state, etc. These factors result in inter-rater variability and less objectivity of the examination [24].

To overcome the limitations of conventional clinical evaluation and diagnosis of HD, researchers have been focusing on computerized quantitative analysis of online handwriting (where each sample is associated to its timestamp [3]) taking advantage of a variety of signal processing and machine learning techniques [14, 1, 34, 33, 25]. In terms of the HD quantification, previous studies [15, 13, 8, 11, 31, 32] have been using conventional feature extraction methods aiming at stroke duration, velocity, acceleration, tilt, pressure, etc.

In our previous works [18, 17, 19], the potential of fractional order derivatives (FD) for development and application of robust and complex kinematic feature extraction methods in the field of Parkinson's disease dysgraphia analysis was uncovered and evaluated. Therefore, we hypothesize that the utilization of FD for the analysis of HD in children population may also bring a noticeable improvement. With this hypothesis in mind, we aim at:

- exploring the utilization of FD in the field of computerized analysis of HD in children population,

- comparing the power of the FD-based features with the set of conventionally used ones to discriminate children without HD and children with HD,
- identifying the optimal range of FD α order for robust and complex quantification of HD.

VI.2 Materials & Methods

VI.2.1 Dataset

In this study, we enrolled 55 children (19 attending 3th grade, and 36 attending 4th grade of primary schools), see Table VI.1 for more information. To assess legibility and performance time during handwriting as well as physical and emotional well-being, the children were asked to fill a self-evaluating Handwriting Proficiency Screening Questionnaire for Children (HPSQ–C) [27]. It contains 10 questions scored on a 5-point Likert scale (0 – no difficulties, 4 – severe difficulties; total score, i. e. sum over all questions: 0 – no HD, 40 – severe HD). The important advantage of HPSQ–C is its language independence and the fact that it has already been validated in a couple of previous studies [32, 14, 2, 34]. Based on the HPSQ–C cut-off scores, the children were separated into two groups: a) children with HPSQ–C < 7 were considered as healthy controls (HC, i. e. no HD); b) children with HPSQ–C $>= 19$ were considered as children with handwriting difficulties (HD). Some of the children, that obtained HSPQ–C scores between these two values, had to be moved into HC or HD group based on the visual inspection of their handwritten product by an independent therapists.

Parents of all the children participating in this study signed an informed consent form, and trough the entire duration of the study, we followed the Ethical Principles of Psychologists and Code of Conduct released by the American Psychological Association (`https://www.apa.org/ethics/code/`).

VI.2.2 Data Acquisition

To record the handwriting process, the children were asked to write all 34 letters of the Czech alphabet using cursive lower-case letters on a lined A4 paper attached to an active area of digitizing tablet Wacom Intuos Pro L (PTH-80) (sampling frequency $f_s = 150\,\mathrm{Hz}$), which enabled us to not only inspect the written product but also to record a variety of signals describing the handwriting process: x and y position ($x[n]$ and $y[n]$); timestamp ($t[n]$); a binary variable ($b[n]$; 0 – in-air movement, i. e. movement of pen tip up to 1.5 cm above the tablet's surface, and 1 – on-surface movement, i. e. movement of pen tip on the paper), pressure exert on the tablet's

Table VI.1: Demographic Characteristics of the Cohort.

clin	mean ± std	min	Q1	Q2	Q3	max
			healthy children			
age	9.13 ± 0.68	8.00	9.00	9.00	10.00	10.00
class	3.67 ± 0.48	3.00	3.00	4.00	4.00	4.00
HPSQ–C	7.07 ± 2.29	3.00	5.25	7.00	8.00	12.00
			children with HD			
age	9.20 ± 0.65	8.00	9.00	9.00	10.00	10.00
class	3.64 ± 0.49	3.00	3.00	4.00	4.00	4.00
HPSQ–C	21.88 ± 3.80	19.00	20.00	20.00	22.00	35.00
			all children			
age	9.16 ± 0.66	8.00	9.00	9.00	10.00	10.00
class	3.65 ± 0.48	3.00	3.00	4.00	4.00	4.00
HPSQ–C	13.80 ± 8.04	3.00	7.00	10.00	20.00	35.00

[1] age is expressed in years

[2] dataset consists of 30 healthy children and 25 children with HD

surface during writing ($p[n]$); pen tilt ($a[n]$); and azimuth ($az[n]$). For more information, we refer to [14, 33]. During data acquisition, all children were also using the Wacom Inking pen, which provides visual feedback as well as a feeling of writing by

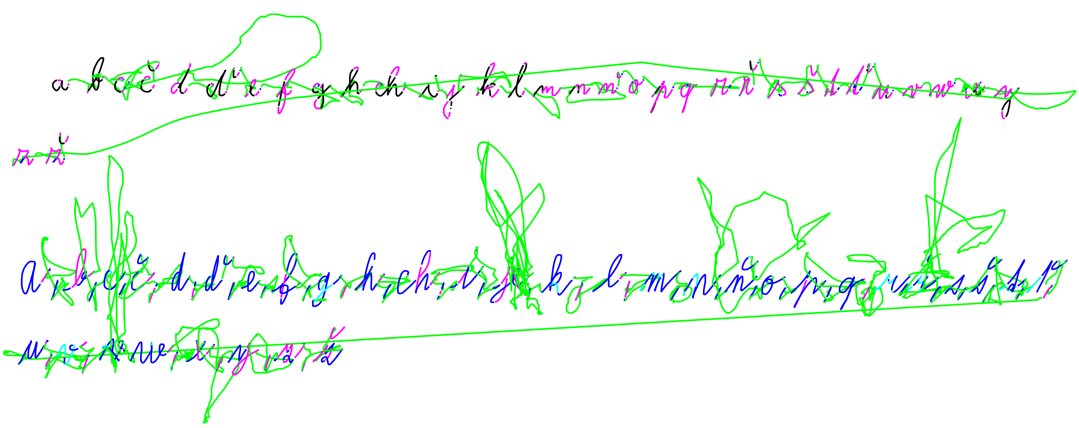

Fig. VI.1: The alphabet written by a 10-year-old girl attending 4th grade (HPSQ–C = 4, the upper part of the figure) and by a 9 years old boy with HD attending 3th grade (HPSQ–C = 30, the lower part of the figure). The four colors represents the actual tip pressure of the inking pen (cyan: 0 – 25 %, blue: 25 – 50 %, purple: 50 – 75 %, black: 75 – 100 %). The in-air trajectories (inking pen above the tablet's surface) of the inking pen are visualized using the light green colour.

a regular inking pen. An example of the written product of the alphabet performed by a HC and a child with HD can be seen in Figure VI.1.

VI.2.3 Fractional Order Derivatives

FD is used as a substitution of the conventional differential derivative during feature extraction. Hereby, we have developed a new advanced approach of handwriting parametrization. FDs have a wide range of settings and several approaches of approximation (e. g. Caputo, Grünwald-Letnikov) [23]. In this work, we utilized the Grünwald-Letnikov approximation implemented by Jonathan Hadida. A direct definition of FD $D^\alpha y(t)$ is based on finite differences of an equidistant grid in $[0, \tau]$ assuming that the function $y(\tau)$ satisfies certain smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid [23]

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{VI.1}$$

with

$$\tau_{k+1} - \tau_k = h \tag{VI.2}$$

and using the notation of the finite differences

$$\frac{1}{h^\alpha}\Delta_h^\alpha y(t) = \frac{1}{h^\alpha}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^\alpha y(\tau_{n+1-v})\right), \tag{VI.3}$$

where

$$c_v^\alpha = (-1)^{v-1}\binom{\alpha}{v}. \tag{VI.4}$$

The Grünwald-Letnikov implementation is defined as:

$$D^\alpha y(t) = \lim_{h \to 0} \frac{1}{h^\alpha}\Delta_h^\alpha y(t), \tag{VI.5}$$

where $D^\alpha y(t)$ denotes a derivative with order α of function $y(t)$, and h represents sampling lattice.

VI.2.4 Handwriting Features

To quantify HD, we used two sets of handwriting features: a) conventional features [14, 10, 26, 9] (used as a baseline feature set); b) features utilizing FD (FD-based features) [18, 17, 19]. Concerning the conventional features, we extracted kinematic (velocity, acceleration, jerk), temporal (duration) and dynamic (azimuth, altitude) ones from both global as well as stroke-based movements. We also used vertical/horizontal projections together with on-surface/in-air trajectories. Finally, we computed number of interruptions in writing and normalized jerk according to [6]. In terms of FD-based features, we extracted basic kinematic features only, namely velocity, acceleration, jerk and their horizontal and vertical variants. All of the features were computed for α in the range of 0.1–0.9 (step of 0.1) except for $\alpha = 1.0$ as it is covered by the conventional feature set . Finally, the statistical properties of all the features from both of the feature sets were described by mean and relative standard deviation (relstd).

VI.2.5 Statistical Analysis

At first, normality of the handwriting features was tested using the Shapiro-Wilk test [30]. Features that were not found to be normally distributed were adjusted using Box-Cox [7] transformation. After that, the distributions of such features were visually re-inspected (some of the features were not fully normalized, however, we hypothesized that such features will not pass the subsequent statistical analysis).

Next, to select only a parsimonious, information-rich subset of the features, we applied a two-step feature selection (FS) before the analysis: a) we used Minimum Redundancy Maximum Relevance (mRMR) [22] algorithm to discard the most redundant features that bring no/very little information; b) we visualized the cross-correlation matrices of the features to discard the ones that have high correlation among each other. With this approach, we reduced the dimension of our feature sets by the following amount: a) conventional feature set: 63 (prior FS), 40 (after FS); and b) FD-based feature set 324 (prior FS), 40 (after FS). The cross-correlation matrices of the best 15 features according to mRMR for both feature sets are visualized in Figure VI.2.

Subsequently, to assess the strength of a relationship between the values of the handwriting features and the clinical status of the children (HC/HD), and the values of the HPSQ–C (severity of HD), Spearman's correlation coefficient [20] with the significance level of 0.05 was computed. Due to the exploratory nature of this study as well as a relatively small number of the features under investigation, no adjustment for multiple comparisons was made.

Finally, to quantify the ability of the handwriting features to discriminate healthy children and children with HD, Mann-Whitney U-test[1] [21] with the significance level of 0.05 between the handwriting features and clinical status of the children (HC/HD) was used.

[1] We did not use Student's t-test because not all features were normally distributed.

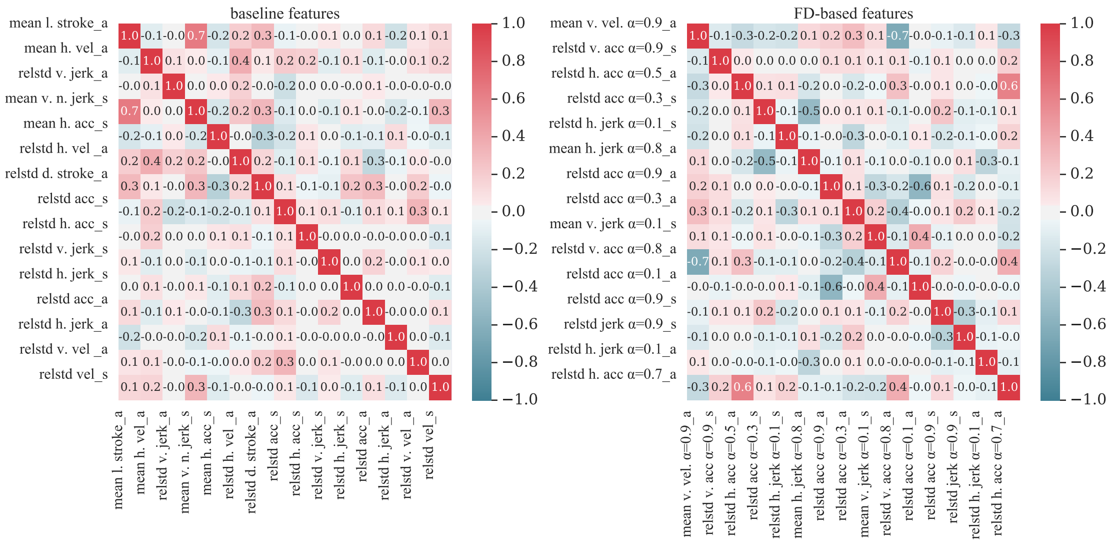

Fig. VI.2: Cross-correlation matrices of the 15 best features selected according to mRMR: a) conventional features (left side); b) FD-based features (right side). Table convention: vel. – velocity; acc. – acceleration; v. – vertical; h. – horizontal; l. – length; n. – normalized; d. – duration; _a – in air movement; _s – on surface movement.

VI.3 Results

The results of the correlation analysis can be seen in Table VI.2. In this table, only statistically significant correlations (i. e. those with the p-value bellow 0.05) are shown. As can be seen, the strongest correlations between the conventional handwriting features and the clinical characteristics of the children were found for the following pair/s[2]: a) $\rho = 0.3220^{*}$ relstd v. acc._s (HC/HD); and b) $\rho = 0.3191^{*}$ mean h. n. jerk_s (HPSQ–C). The strongest correlation for the FD-based features: a) $\rho = -0.3105^{*}$ relstd acc. $\alpha = 0.2$_a (HC/HD); and b) $\rho = -0.3405^{*}$ relstd v. vel. $\alpha = 0.5$_a (HPSQ–C) being the strongest correlated feature-clin. char. pair.

Next, the kernel density estimation plots of the 4 best features selected according to the power to distinguish healthy and impaired handwriting assessed by Mann-Whitney U-test are shown in Figure VI.3 (as well as in the case of the correlation analysis, only the features with the p-value bellow 0.05 were considered). The figure shows both conventional features and FD-based ones: a) conventional feature with the greatest discrimination power: mean l. stroke_a and mean v. n. jerk_s (p = 0.0110); b) FD-based feature with the greatest discrimination power: relstd acc. $\alpha = 0.3$_a (p = 0.0169).

Finally, the distribution of the order of FD (α) across the best 40 FD-based

[2]Correlation with $p < 0.05$ (*), correlation with $p < 0.01$ (**).

Table VI.2: Results of the Correlation Analysis.

handwriting feature	feature type	clin	ρ	p
relstd v. acc._s	Conv	HC/HD	0.3220	0.0165
mean v. n. jerk_s	Conv	HC/HD	0.3128	0.0200
mean l. stroke_a	Conv	HC/HD	0.3128	0.0200
mean h. n. jerk_s	Conv	HC/HD	0.2990	0.0266
relstd azimuth	Conv	HC/HD	0.2829	0.0363
mean h. n. jerk_s	Conv	HPSQ–C	0.3191	0.0176
mean v. n. jerk_s	Conv	HPSQ–C	0.3058	0.0232
mean d. stroke_a	Conv	HPSQ–C	0.3054	0.0234
relstd azimuth	Conv	HPSQ–C	0.3040	0.0241
relstd v. acc._s	Conv	HPSQ–C	0.2798	0.0385
relstd acc. $\alpha = 0.2$_a	FD-based	HC/HD	-0.3105	0.0210
relstd acc. $\alpha = 0.3$_a	FD-based	HC/HD	-0.2898	0.0318
relstd v. vel. $\alpha = 0.5$_a	FD-based	HPSQ–C	-0.3405	0.0110
relstd acc. $\alpha = 0.3$_a	FD-based	HPSQ–C	-0.3150	0.0192
relstd acc. $\alpha = 0.2$_a	FD-based	HPSQ–C	-0.2990	0.0266

[1] clin – clinical characteristics, i. e. dependent variable (clinical state: HC/HD, values of HPSQ–C); ρ – Spearman's correlation coefficient; p – p-value of ρ; Conv – conventional feature set; FD-based – FD-based feature set; vel. – velocity; acc. – acceleration; v. – vertical; h. – horizontal; l. – length; n. – normalized; d. – duration; _a – in air movement; _s – on surface movement.

features selected according to mRMR is drawn in Figure VI.4.

VI.4 Discussion

The correlation analysis (see Table VI.2) for FD-based features shown that there is a statistically significant relationship between HPSQ–C and relative standard deviation of vertical velocity with α of 0.5, which is in line with the results of [13] reporting that vertical in-air velocity might be a potential biomarker for HD identification. With respect to the comparison between the two feature sets, it can be seen that all relevant FD-based features are related with in-air trajectories, more specifically with acceleration and velocity that probably points out to their capability of quantifying hesitating and dysfluent movements during stroke interruptions, which is also coherent with our previous studies [34, 14]. In contrast, three out

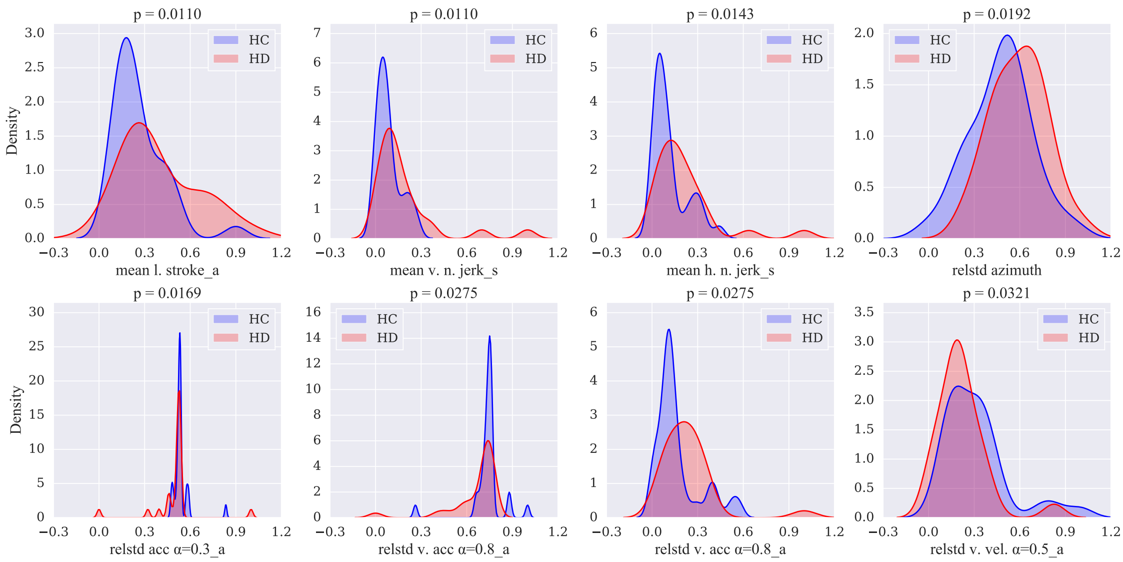

Fig. VI.3: Kernel density estimation plots of the 4 best features ranked by Mann-Whitney U-test: a) baseline (conventional) features (upper part); b) FD-based features (bottom part). Features are visualized separately for healthy children (HC) and children with HD. On top of each figure, the corresponding p-value is shown. All features were normalized using min-max normalization (min $= 0$, max $= 1$) prior the plotting. Figure convention: vel. – velocity; acc. – acceleration; v. – vertical; h. – horizontal; l. – length; n. – normalized; d. – duration; _a – in air movement; _s – on surface movement; p – p-value of Mann-Whitney U-test.

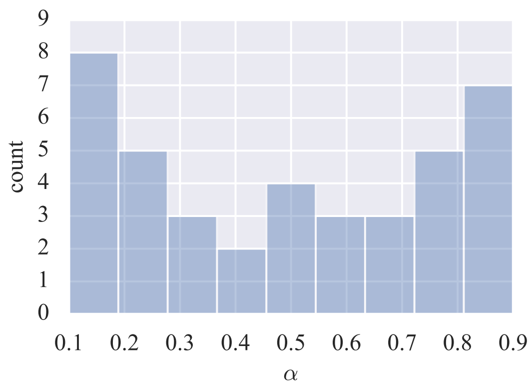

Fig. VI.4: Distribution of the FD order (α) across the best 40 FD-based features selected according to mRMR (feature selection step applied prior to the analysis).

of the total number of four selected conventional features were computed from the on-surface movements. An important observation to note is the presence of relative standard deviation of azimuth showing that even for a relatively automated task such as the Alphabet writing, the lack of fine motor control together with redundant wrist movements are present in children with HD [28, 29]. Finally, all selected FD-based features have α between 0.2 and 0.5, which suggest that regular derivation is not optimal for temporal handwriting features (acceleration and vertical stroke velocity) and that FD is likely to improve their ability to describe HD.

Regarding the results of Mann-Whitney U-test (see Figure VI.3), they suggest that the alphabet handwriting task is not very suitable for discrimination of HC and children with HD. When looking at the shape of the probability density function for the 4 selected features in both feature groups, it is obvious that a single feature will not have sufficient discrimination power. With respect to FD-based features, those derived from the acceleration of in-air movements emerged as the most significant ones. This may refer to the difficulties in writing of particular characters of the alphabet, such as long preparation, hesitancy, distress, etc., which can also be seen when inspecting the shapes of the particular characters in the example provided in Figure VI.1. It is evident that for the child with HD, the on-surface movements are more or less without visible corruptions. However, the difference is eminent for the movements above the tablet's surface.

According to the distribution of the FD α order across the handwriting features that passed the FS (see Figure VI.4), we were able to identify its optimal range for HC/HD discrimination: 0.1–0.3, and 0.7–0.9, which is also supported by the results of the statistical analysis (the features with the greatest discrimination power and the most statistically significant correlation were computed using the α values from one of those two ranges) and is also in line with our previous study [16] in which we focused on the FD optimization for Parkinson's disease dysgraphia and obtained similar α ranges (0.05–0.45, and 0.6–0.8). Altogether, we can hypothesize there exists some universal optimal range of α suitable for the analysis of corrupted handwriting performance via online handwriting quantification that we need to search for.

VI.5 Conclusion

To the best of our knowledge, this is the first study that performs an investigation of the possibilities of using FD in the computerized assessment of HD in school-aged children. We can conclude that FD-based features bring benefits of more robust quantification of in-air movements as opposed to the conventionally used ones. These movements are likely to describe inter-stroke hesitation/s, uncertainty during writing, stiffness of hand/fingers, etc., which can definitely be linked with HD and are imperceptible to an examiner that only sees the written product (even computerized approaches, if not sensitive enough, can be incapable of the precise description of such phenomena).

Although we have shown that utilization of FD can be beneficial for a computerized assessment of HD, several limitations need to be pointed out too. First of all, the alphabet task does not seem to be optimal for the differential analysis, as some of the children's handwriting capabilities and habits are not fully quantified (e. g. copying/writing of words, sentences or paragraphs requires continuous writing, simple graphomotor elements require the application of children's drawing skills, etc. [32, 4]). Next, our dataset consists of only 55 subjects, which is a relatively small number in terms of the statistical validity of the results. Moreover, grouping children in two subject groups (HC/HD) was based entirely on the selection of a cut-off score applied on HPSQ–C, which may not reflect the true nature/presence of HD.

In our future studies, more granular FD α order search (step of 0.01 or even less) as well as investigation of other FD approximations (e. g. Capputo's approximation) will be analyzed. Finally, to investigate the power of FD-based features to not only discriminate HC/HD but also predict the presence/severity of HD in children population, advanced classification and regression models will be trained and evaluated.

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VII Advanced Parametrization of Graphomotor Difficulties in School-aged Children

Outline

Bibliographic Information

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Author's Contribution

The author proposed a new method usage, co-designed and co-performed the analysis, and wrote a part of the manuscript. He was also working on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

School-aged children spend 31–60 % of their time at school performing handwriting, which is a complex perceptual-motor skill composed of a coordinated combination of fine graphomotor movements. As up to 30 % of them experience graphomotor difficulties (GD), timely diagnosis of these difficulties and therapeutic intervention are of great importance. At present, an objective, computerized decision support system for the identification and assessment of GD in school-aged children is still missing. In this study, we propose three novel advanced handwriting parametrization techniques based on modulation spectra, fractional order derivatives, and tunable Q-factor wavelet transform to improve the identification of GD using online handwriting. For this purpose, we analyzed signals acquired from 7 basic graphomotor tasks performed by 53 children attending 3rd and 4th grade at several primary schools around the Czech Republic. Combining the newly proposed features with the conventionally used ones, we were able to identify GD with 84 % accuracy. In this study, we showed that using advanced parametrization of basic graphomotor movements can be potentially used to improve our capabilities of quantifying problems with the development of legible, fast-paced handwriting, and help with the early diagnosis of handwriting difficulties frequently manifested in developmental dysgraphia.

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VII.1 Introduction

At present, every school-aged child is expected to master legible, well-coordinated and fast-paced handwriting, which is a complex perceptual-motor skill learned by instruction that quantifies a child's timely maturation and integration of psychomotor, linguistic and mental abilities, and readiness for education [21]. It is known that it takes approximately 10 years to develop handwriting skills [2] on both quantitative (speed) and qualitative (legibility) level [9, 59]. However, before a child starts to write, she/he first needs to learn how to draw [31]. In general, until the age of 6, a child starts to develop a combination of motor and non-motor skills such as motor planning and execution, visual–perceptual abilities, orthographic coding, kinesthetic feedback, and visual–motor coordination, which eventually become automated at the age of 8–9 [27, 48]. These skills are referred to as graphomotor skills (GS) [4, 20], and form the foundation of drawing and consequently, handwriting abilities [2] that accompany every person throughout the life-time.

Even though modern technologies brought new ways of communication, self-expression, and education, handwriting is still an important part of a child's life [20]. In general, it has been estimated that children spend 31–60 % of their school-time performing handwriting [33]. Given that children at school need to write under time constraints, the acquisition of GS is crucial for a child's ability to write legibly, as well as quickly and efficiently. Basically, the development of GS affects a child's academic success and professional career [19]. It has also been shown that approximately 10–30 % of children experience graphomotor difficulties (GD) [20, 4] such as motor-memory dysfunction (problems combining memory input with motor output), graphomotor production deficits (poor muscle coordination, unusual pen-grip and less precise graphomotor movements), motor feedback difficulties (over-activation of certain muscles and joints during handwriting as well as problems tracking the location of the pen's tip), etc. Such an impairment of the neuro-muscular system can have serious pedagogical and psychological consequences, and can greatly affect a child's every-day life [22] starting with slow and less-legible handwriting, lack of motivation to write, lower self-esteem combined with poor emotional well-being, bad attitude and behaviour, communication and social interaction problems, and in some cases going as far as being diagnosed with a serious neurodevelopmental disorder such as developmental dysgraphia (DD) [64, 20, 44, 34]. To provide children with both preventive as well as corrective therapeutic care, GD should be identified and treated as soon as possible [14, 30].

To identify and evaluate GD and handwriting difficulties (HD) in general, occupational therapists and/or special educational counsellors use specialized questionnaires or tests that aim at quantification of the quality of the handwritten product in multiple domains using its visual inspection. Some of the most commonly used questionnaires (rating scales) are the following: Concise Assessment Scale for Children's Handwriting (Brave Handwriting Kinder) (BHK) [24], Handwriting Proficiency Screening Questionnaire (HPSQ) [47] or Handwriting Proficiency Screening Questionnaire for Children (HPSQ–C) [51]. Even though these scales are a well-established way of identification and rating of GD and HD in school-aged children, its administration and coding are time-consuming, which limits the use of this type of evaluation on a regular day-to-day basis. Moreover, it is naturally limited by the perceptual capabilities, subjective judgement and experience of an examiner [57]. Finally, it is also subject to inter-rater variability [15]. Due to the complexity and limitations associated with GD/HD identification, many children, especially those attending lower grades of a primary school, may remain undiagnosed or may be diagnosed later than appropriate.

To overcome the limitations of the perceptual analysis and search for a more robust view of various hidden complexities of the handwriting process, new methods based on digitization and signal processing techniques have been developed [58, 52, 55, 49, 43, 7]. More specifically, instead of a conventional data acquisition using a pen and paper, digitizing tablets (digitizers) have been used to record a variety of signals describing the evolution of handwriting in time. Such a collection of data about handwriting (i. e. that one associated with timestamps) is referred to as online handwriting [5]. Using advanced digital signal processing algorithms a variety of handwriting parameters (commonly referred to as handwriting features) quantifying kinematic (velocity, acceleration, jerk) as well as dynamic (pen pressure, tilt and azimuth) components contributing to the execution of the handwriting process have been designed [27, 50, 28, 35]. Such characteristics are very hard to be perceived and precisely quantified by a human observer and are almost impossible to be extracted using only the final handwritten product.

In recent years, several studies focusing on computerized analysis, identification and assessment of HD, mostly associated with writing in children with developmental dysgraphia, have been conducted. In 2017, Pagliarini *et al.* [43] reported that the governing principles of rhythmic organization, namely homothety and isochrony, describe the handwriting process in school-aged children from the time where the very first handwritten products are made, i. e. before the handwriting is performed automatically. Moreover, they pointed out the potential of quantitative analysis to indicate the development of HD at a very early age. In the same year, Mekyska *et al.* [35] performed a study in a cohort of 27 school-aged children in which they introduced a new intra-writer normalisation method aiming at improving the discrimination capabilities of a large variety of conventional and non-conventional handwriting features. They also built a random forest classifier identifying the presence of DD with

96 % sensitivity and specificity. Next, Rosenblum and Dror [49] employed a study focusing on automatic identification and characterization of DD in a cohort of 99 third-grade children. Using various kinematic and dynamic features, they trained a linear support vector machines classifier achieving 90 % sensitivity and specificity. In 2018, Asselborn *et al.* [7] developed a diagnostic tool for DD evaluated on a cohort of 298 children (56 children with DD) performing the BHK test on a digitizing tablet covered with a sheet of paper. To identify the presence of DD, they computed 53 handwriting features and built a random forest classifier with 96 % sensitivity and 99 % specificity. In 2019, Mekyska *et al.* [36] employed a study that is the closest one to a study proposed in this work. They aimed at exploring the impact of specific elementary graphomotor tasks on the accuracy of computerised diagnosis of GD. For this purpose, they analysed 7 basic graphomotor elements performed by a cohort of 76 school-aged children. Using only conventional handwriting features, they trained an XGBoost [13] classifier and achieved 50 % sensitivity and 90 % specificity. In the same year, Zvoncak *et al.* [71] used features based on fractional order derivatives to enrich a set of conventional features and analysed their correlation with HPSQ–C in 55 children (19 third-grade children, and 36 fourth-grade children) performing an alphabet writing task. With this setup, they reported that features based on fractional order derivatives improved quantification and robustness of the description of in-air movements. And finally, in 2020 Asselborn *et al.* [6] proposed a data driven strategy for estimating handwriting quality in a battery of 448 school-aged children (390 typically developing children and 58 children with HD). They utilized principal component analysis to reduce 53 handwriting features also used in [7] to three dimensions that are independent of the BHK scores. Next, they used the reduced feature space to cluster children into two groups (typical handwriting, HD), and evaluated how far a child's score is from the average score of children of the same age and gender. With this approach, they reported four specific handwriting scores for kinematics, pressure, pen tilt and static features to describe the handwriting profile of a child in a finer way that enables measuring the quality of handwriting in multiple domains.

Although there is a body of research dealing with computerized quantitative analysis of HD in school-aged children, several key points have not been fully investigated yet. First of all, most of the studies aimed at identifying HD and/or DD. Studies focusing on quantification and identification of GD are very sparse. This is an important topic as HD can have many forms and can vary even among typically developing children. As mentioned in one of the most recent publications dealing with computerized analysis of handwriting in school-aged children proposed by Asselborn *et al.* [6], dysgraphia is an umbrella term that describes a variety of handwriting difficulties. Therefore, GD play a crucial role in determining the handwriting profile of a child, and should be investigated as well. Moreover, most of the studies focused on writing signals such as writing words, sentences, etc., only. Finally, conventional handwriting features have been used to describe HD almost exclusively. To the best of our knowledge, a comprehensive study aiming at quantifying GD manifested during performing a battery of simple but important graphomotor elements (loops, spirals, etc.) using not only conventional but also more advanced graphomotor features is missing. For this purpose, in this study, we propose the use of seven graphomotor tasks and three novel types of handwriting features based on: a) modulation spectra; b) fractional order derivatives; and c) tunable Q-factor wavelet transform. We hypothesize that these features can bring more information about specific GD accompanying the handwriting process of children with GD in its very basis. In addition, we also hypothesize that a combination of conventional and more advanced parametrization of online handwriting can improve identification of GD and contribute to a development of a decision support system that can be used for diagnosis of HD and eventually DD.

VII.2 Materials and Methods

The methodology can be briefly summarized as follows: a) dataset description (cohort, acquisition protocol, data acquisition, etc.), b) presentation of the feature extraction methods (conventional, newly-proposed features), and c) statistical analysis and machine learning (normality testing and feature pre-processing, feature selection, correlation analysis, hypothesis testing, and binary classification). Finally, an overview of the methodology can also be seen in Fig. VII.1.

VII.2.1 Dataset

Altogether, we enrolled 53 Czech-speaking children (22 girls and 31 boys) attending 3rd and 4th grade at several primary schools in the Czech Republic: 26 healthy children (HC) (2 3rd-grade girls, 12 4th-grade girls, and 12 4th-grade boys) and 27 children with GD (1 3rd-grade girl, 5 3rd-grade boys, 7 4th-grade girls, and 14 4th-grade boys). Description of the dataset can be seen in Table VII.1. During the data acquisition, all of the children were asked to perform a specifically designed drawing protocol consisting of 7 elementary graphomotor tasks (TSK) (for more information, see Fig. VII.2): TSK1 – Archimedean spiral (approximately 15 cm in height); TSK2 – half-sized version of TSK1; TSK3 – connected loops; TSK4 – flipped version of TSK3; TSK5 – sawtooth; TSK6 – rainbow; TSK7 – combination of TSK3 and TSK4. Each of the tasks was first shown to a child and then she/he replicated it on a blank sheet of paper with a comfortable speed. The protocol was designed

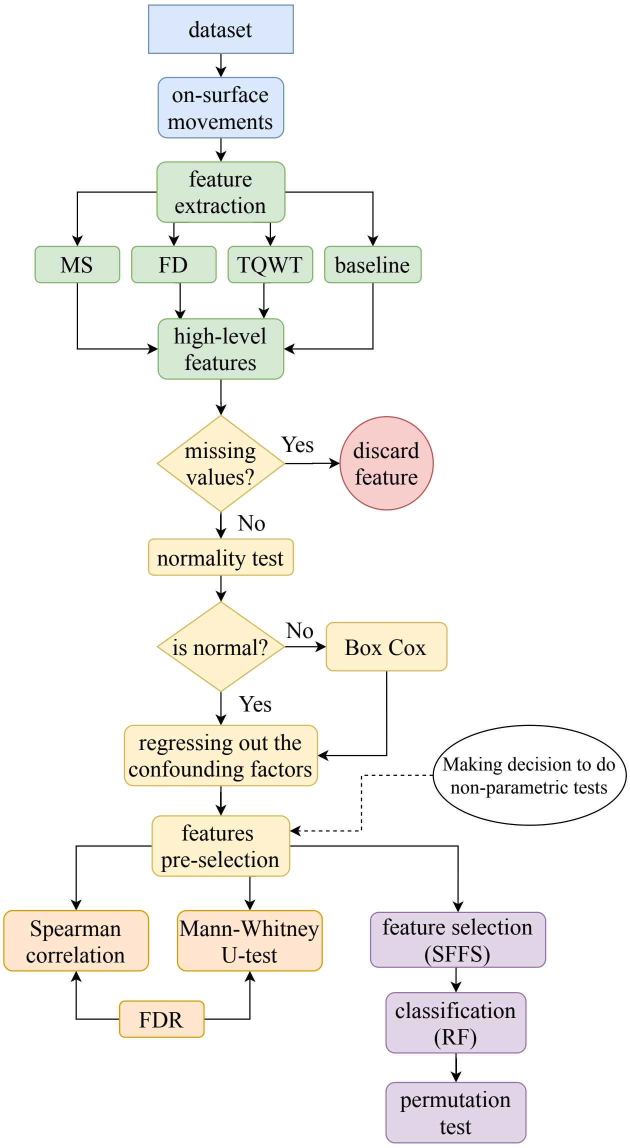

Fig. VII.1: An overview of the methodology applied in the study.

in cooperation with psychologists and special educational counsellors so that it reflects all coordinated elementary movements that are needed to successfully write cursive letters (i. e. cursive letters are constructed of these basic graphomotor elements, therefore, mastering these elements is a prerequisite for mastering legible handwriting). Examples of the final handwritten product for all graphomotor tasks performed by healthy children and children with GD can be seen in Fig. VII.3.

The protocol was printed on an A4 paper that was laid down and fixed to a digitising tablet. To acquire the handwriting data, we used Wacom Intuos Pro L (PHT-80) with the sampling frequency of 150 Hz, and a Wacom Inking pen. This set-up enabled us to take advantage of two facts: a) it provided the children as well as an examiner with immediate visual feedback and made it possible to simulate the feel-

Table VII.1: Description of the dataset.

	μ (σ)	min.	Q1	Q2	Q3	max.
all children (53 subjects)						
age [y]	10.92 (1.65)	8.46	10.73	11.33	11.67	12.32
class	3.84 (0.36)	3.00	4.00	4.00	4.00	4.00
HPSQ–C	13.66 (6.31)	4.00	9.00	12.00	19.00	27.00
HC (26 subjects)						
age [y]	11.23 (0.62)	9.77	10.99	11.43	11.66	12.32
class	3.92 (0.27)	3.00	4.00	4.00	4.00	4.00
HPSQ–C	12.50 (6.21)	4.00	9.00	10.50	14.00	27.00
GD (27 subjects)						
age [y]	10.57 (2.19)	8.46	10.52	10.95	11.66	12.27
class	3.77 (0.42)	3.00	4.00	4.00	4.00	4.00
HPSQ–C	14.44 (6.30)	6.00	10.00	13.00	19.50	25.00

[1] μ – mean estimate; σ – standard deviation estimate; HPSQ–C – Handwriting Proficiency Screening Questionnaire for Children [51] (only total score showing an overall degree of GD is shown); Qx – x-th quartile; y – years.

ing of using a conventional inking pen; and b) it allowed for recording of a variety of signals describing the drawing process: x and y position ($x[n]$ and $y[n]$); timestamp ($t[n]$); a binary variable ($b[n]$; 0 – in-air movement, i. e. movement of pen tip up to 1.5 cm above the tablet's surface, and 1 – on-surface movement, i. e. movement of pen tip on the paper), pressure exert on the tablet's surface during drawing/writing ($p[n]$); pen tilt ($a[n]$); and azimuth ($az[n]$). For more information, we refer to our previous works [35, 69].

Moreover, to assess legibility and performance time during handwriting as well as physical and emotional well-being, the children were asked to evaluate themselves using HPSQ–C (rating scale) [51], which is composed of 10 questions scored on a 5-point Likert scale (0 – never, i. e. no GD, 4 – always, i. e severe GD; total score, i. e.

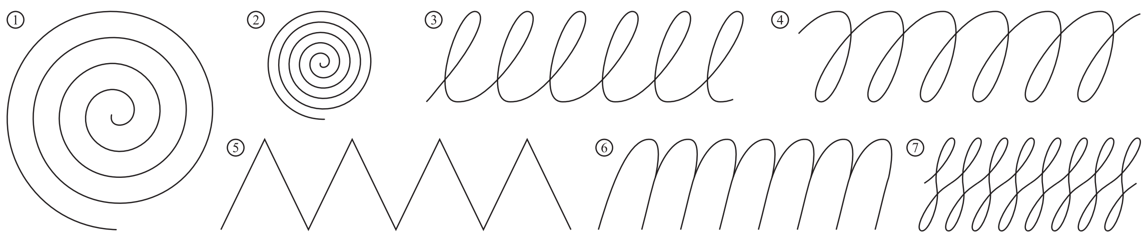

Fig. VII.2: Drawing acquisition protocol with the selected graphomotor tasks.

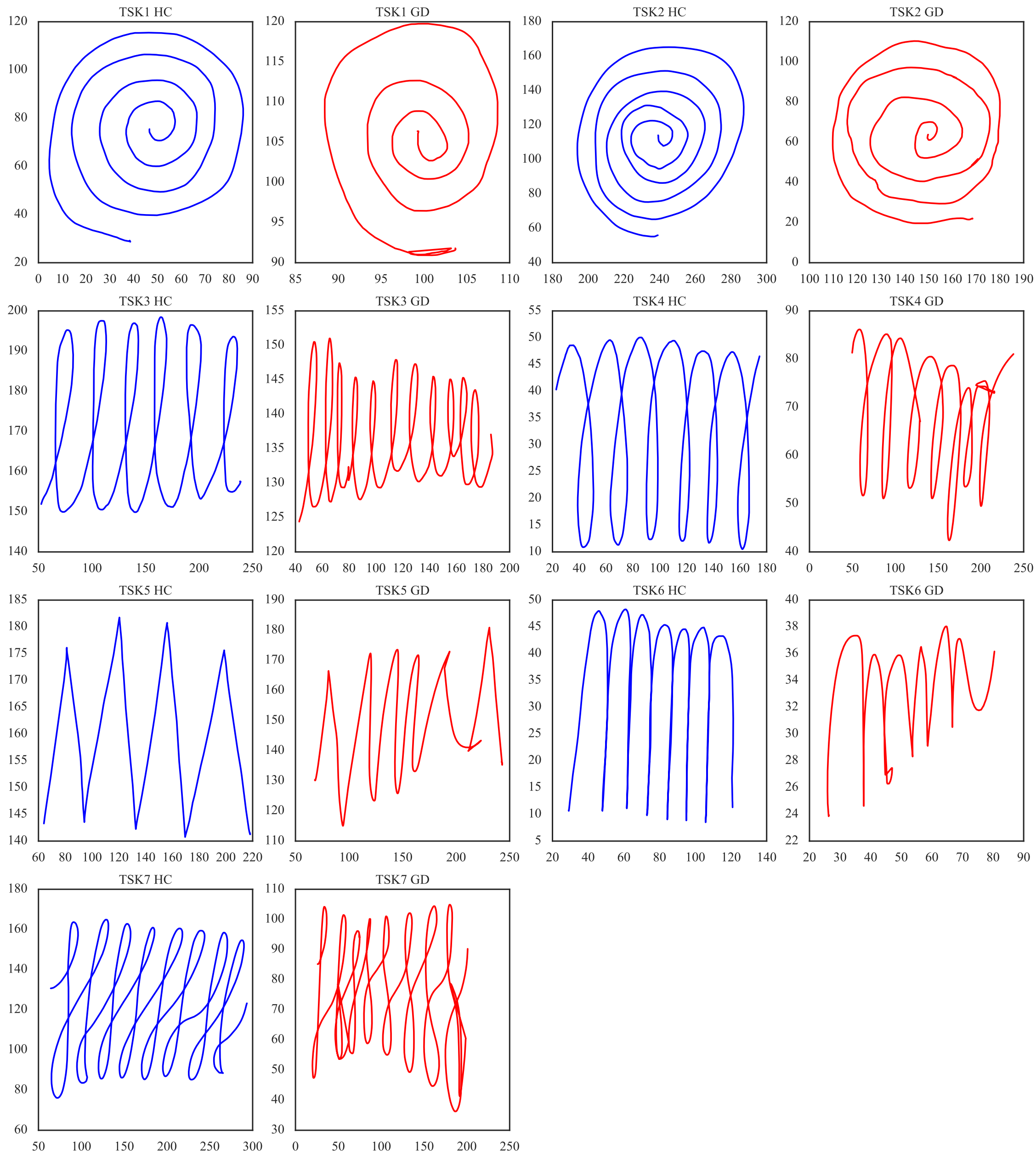

Fig. VII.3: Example of the final handwritten product for all graphomotor tasks performed by randomly selected healthy children (blue) and children with GD (red) (units are in millimeters).

sum over all questions: 0 – min. value, 40 – max. value; legibility – items 1, 2, and 10, performance time – items 3, 4 and 9, and physical and emotional well-being – items 5–8). Using HPSQ–C brings two important advantages: a) the scale is language independent and therefore well-comparable across studies employed on cohorts coming from different language groups; b) it has already been validated in a couple of previous studies such as [68, 35, 4, 70]. The overall HPSQ–C scores, as well as the final handwritten product, were both examined by experienced psychologists and special educational counsellors. The decision about a child's assignment into HC or GD group was performed on a PC after the examination of a child's handwritten product, where an expert (remedial teacher) had no information about her/his sociodemographic information (e. g. sex, class, HPSQ–C, etc.). The description of HC/GD groups mentioned at the beginning of Section VII.2 presents the numbers after the final examination and assignment.

Parents of all children participating in this study signed an informed consent form approved by the Ethical Committee of the Masaryk University. Throughout the entire duration of this study, we strictly followed the Ethical Principles of Psychologists and Code of Conduct released by the American Psychological Association (https://www.apa.org/ethics/code/).

VII.2.2 Feature extraction

To quantify GD, we extracted the following conventionally used graphomotor features (CONV) [54, 50, 55]: a) spatial features – width (WIDTH), height (HEIGHT), and length (LEN) of the signals (also referred to as writing). Even though the in-air movements can be used to capture a certain aspect of GD [53, 54], all graphomotor tasks proposed in this work should be performed using a single stroke. Since the number of multi-stroke signals analyzed in this study was only marginal, we did not distinguish between signals and strokes and used the stroke notation, i. e. stroke width (SWIDTH), height (SHEIGHT), and length (SLEN), as it is used in general; b) kinematic features (horizontal and vertical projection) – velocity (VEL), acceleration (ACC), and jerk (JERK); and c) dynamic features – pressure (PRESS), tilt (TILT), and azimuth (AZIM). These features were used as a baseline feature set. To build on top of these conventional features and to enhance their capability of describing GD in a more robust and complex way, we present three new feature-types aiming at improving the quantification and description of GD in school-aged children, namely: a) features based on modulation spectra (MS); b) features based on fractional order derivatives (FD); and c) features based on tunable Q-factor wavelet transform (TQWT). All vector-valued features were transformed to scalar values using mean and coefficient of variation (cv) estimates (some of the novel features used additional statistical functions that are described along with the features themselves).

An important fact to point out is that these features were designed not only to improve the robustness of the conventional features but also to maintain as much interpretability as possible. This is crucial especially for their real use in clinical practice because the complexity and great discrimination power without understanding the meaning of the features are not likely to bring trust and convenience. If psychologists and special educational counsellors are able to link the features with the specific physiological phenomena, the computerized quantitative analysis of GD can be finally deployed.

To present the features in a compact and easy to read way, we used the following naming convention: *TSK INF: DIR-FN (HL)*, where *TSK* denotes the specific graphomotor task, *INF* represent information about the movement (ON – on-surface, AIR – in-air), PRESS – pressure, TILT – tilt, and AZIM – azimuth), *DIR* stands for direction (H – horizontal and V – vertical), *FN* shows the feature name, and *HL* holds an applied statistic (if any). Moreover, each specific novel feature-type also sets *FN* accordingly (described in the section devoted to the proposed features). As all features presented in this work are computed from on-surface movements, the on-surface/in-air information is considered redundant and is not shown in the feature names.

VII.2.2.1 Modulation spectra features

The first type of the novel features proposed in this work is based on modulation spectra as a non-parametric method for representing modulations in an analyzed biomedical signal. MS has already been used for parametrization of dysarthric speech in patients with Parkinson's disease (PD) [37]. These features however aimed at describing instability of vocal folds vibrations. The features proposed in this work aim at quantifying the ratio between the low and high-frequency movements present in a given handwriting signal of children attending a primary school.

To compute the modulation spectra features, Short-Time Fourier Transform (STFT) of the input handwriting signal $s[n]$ of length N is computed as

$$\begin{gathered} S[k,m] = \sum_{n=0}^{N-1} s[n]w[n-mL]\mathrm{e}^{-\mathrm{j}k\frac{2\pi}{N}n}, \\ k = 0,1,\ldots,N-1, \\ m = 0,1,\ldots,M-1, \end{gathered} \tag{VII.1}$$

where M denotes the number of segments obtained using a segmentation window $w[n]$ composed of L samples. In the frame of this work, we used Hamming segmentation windows with $L = 75$ samples ($f_s = 150\,\mathrm{Hz}$, windows of 0.5 s with the overlap of 50 %).

Next, power spectrum $|S[k,m]|^2$ of each segment is computed and filtered by a filer-bank P consisted of P_n filters. For this purpose, we used a filter bank of 50 linearly distributed triangular filters. After the filtration, the matrix $X[p,m]$ contains P_n sub-bands $p = 1, 2, \ldots, P_n$. Subsequently, each sub-band is normalized [29] as follows

$$\hat{X}[p,m] = \ln\left(X[p,m]\right) - \overline{\ln\left(X[p,m]\right)}, \tag{VII.2}$$

where $\overline{*}$ refers to the averaging operator applied over m.

To obtain a modulation spectra matrix, Discrete Fourier Transform (DFT) is applied on $\hat{X}[p,m]$.

$$\Psi[p,l] = \sum_{m=0}^{M-1} \hat{X}[p,m] \mathrm{e}^{-\mathrm{j}l\frac{2\pi}{M}m}, \tag{VII.3}$$
$$l = 0, 1, \ldots, M-1,$$

where p and l denote the handwriting and modulation frequency, respectively. Finally, $\Psi[p,l]$ is normalized by the mean of each sub-band.

After obtaining the modulation spectra matrix, a vector of handwriting cut-off frequencies $f_c = 1, 2, \ldots, C\,[\mathrm{Hz}]$ is defined. The values of f_c are subsequently converted to the filter indices c using their center frequencies. In this work, we used $f_c \in F_c$, where $F_c = 1, 2, \ldots, 10, 15, 20, 25\,\mathrm{Hz}$. Next, for each value of f_c, low (E_l) and high frequency (E_h) summation components of $\Psi[p,l]$ are computed as

$$E_{l(f_c)}[l] = \sum_{p=0}^{c} \Psi[p,l], \tag{VII.4}$$

$$E_{h(f_c)}[l] = \sum_{p=c}^{P_n} \Psi[p,l], \tag{VII.5}$$
$$l = 0, 1, \ldots, M-1,$$
$$fc = F_c.$$

Finally, $E_{l(f_c)}$ and $E_{h(f_c)}$ are used to compute the final energy ratio R_{f_c} between the low and high frequency movements in the analyzed handwriting signal. It is defined as

$$R_{f_c} = \frac{\sum\limits_{l=0}^{M-1} E_l[l]^2}{\sum\limits_{l=0}^{M-1} E_h[l]^2}. \tag{VII.6}$$

We used the following naming convention for the MS features: $F\mathrm{R}f_c$, where F represents the name of the handwriting feature, R stands for ratio, and f_c holds the value of the specific handwriting cut-off frequency used to compute the energy ratio.

VII.2.2.2 Fractional order derivative features

The second type of the novel features is based on the theory of fractional order derivatives. Handwriting features based on FD have already been explored in our previous studies focusing on the quantitative analysis of parkinsonian dysgraphia [38, 41, 39, 40], where they brought a promising improvement in the power of the FD-based features to objectively discriminate between healthy and dysgraphic handwriting using machine learning. In this work, we aim at exploring the possibilities of utilizing FD to describe GD in school-aged children.

The most common approaches to compute FD are Riemann–Liouville, Caputo, and Grünwald–Letnikov formulations [66, 46, 26]. Parameterization of online handwriting using FD is performed by substituting the conventional differential derivative during the calculation of the basic kinematic features (velocity, acceleration, and jerk). The advantage of FDs lies in their wide range of settings (order α, kernel function, etc.). In this study, we followed the Grünwald–Letnikov approximation [60, 46] and used the implementation of FD by Jonathan Hadida. To decrease the computational requirements, we used a segmentation-based computation.

A direct definition of the $D^{\alpha}y(t)$ is based on the finite differences of an equidistant grid in $[0, \tau]$, assuming that the function $y(\tau)$ satisfies certain smoothness conditions in every finite interval $(0, t), t \leq T$. Choosing the grid [46]

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{VII.7}$$

with

$$\tau_{k+1} - \tau_k = h \tag{VII.8}$$

and using the notation of finite differences

$$\frac{1}{h^{\alpha}}\Delta_h^{\alpha}y(t) = \frac{1}{h^{\alpha}}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^{\alpha} y(\tau_{n+1-v})\right), \tag{VII.9}$$

where

$$c_v^{\alpha} = (-1)^{v-1}\tbinom{\alpha}{v}. \tag{VII.10}$$

The Grünwald–Letnikov definition from 1867 is defined as

$$D^{\alpha}y(t) = \lim_{h \to 0} \frac{1}{h^{\alpha}}\Delta_h^{\alpha}y(t), \tag{VII.11}$$

where $D^{\alpha}y(t)$ denotes a derivative with order α of a function $y(t)$, and h represents a sampling lattice. Following our previous works focused on optimization of α [40, 38], we used the ranges: from 0.1 to 0.4, and from 0.65 to 0.9, with iteration step of 0.05.

The naming convention for FD-based features can be described as: $F\alpha$, where F represents the name of the handwriting feature and α stands for the order of FD.

VII.2.2.3 Tunable Q-factor wavelet transform features

The last type of the novel features is based on tunable Q-factor wavelet transform [61, 62, 8]. Recently, we have shown that HD manifest themselves in higher energies of the residual component of the decomposed signal computed by TQWT [70]. Following our previous research, we aim at investigating the potential of TQWT to describe limited motor skills, poor dexterity and muscle tone or unspecified motor clumsiness in school-aged children suffering from GD.

TQWT is a non-linear discrete-time resonance-based signal decomposition technique that separates an input signal into high-resonance (sustained rhythmic oscillations), low-resonance (non-rhythmic and transient behaviour) and residual components (stochastic nature of the decomposed signal) [61]. It is parameterized by a tunable Q-factor and an oversampling rate (redundancy). In this study, we utilized the implementation of TQWT based on morphological component analysis (MCA) [65] and split augmented Lagrangian shrinkage algorithm (SALSA) [3] described in [62].

To decompose an input signal into high and low resonance components, an iterative J-level decomposition of its low-pass channel by a two-channel filter-bank composed of low- and high-pass filters is used [62]. The frequency responses of the low-pass $H_l(\omega)$ and the high-pass $H_h(\omega)$ filters are defined as

$$H_l(\omega) = \theta \frac{\omega + (\beta - 1)\pi}{\alpha + \beta - 1}, \tag{VII.12}$$

$$H_h(\omega) = \theta \frac{\alpha\pi - \omega}{\alpha + \beta - 1}, \tag{VII.13}$$

for $(1-\beta)\pi < \omega < \alpha\pi$, where α and β are the low- and high-pass scaling parameters, and θ is the Daubechies frequency response [62] given as

$$\theta(\omega) = 0.5(1 + \cos\omega)\sqrt{2 - \cos\omega}, \tag{VII.14}$$

for $\mid \omega \mid \leq \alpha$. More details can be found in [61, 62].

To describe the proposed features, we define the clean graphomotor signal $x_c[n]$ as

$$x_c[n] = x[n] - x_r[n], \tag{VII.15}$$

where $x[n]$ is a handwriting signal, and $x_r[n]$ is a residual signal given as $x_r[n] = x[n] - x_h[n] - x_l[n]$ ($x_h[n]$ and $x_l[n]$ are the high- and low-resonance components).

With $x_c[n]$ and $x_r[n]$ being defined, the signal-to-noise ratio is computed as

$$SNR = 10 \log_{10} \left(\frac{E(x_c[n])}{E(x_r[n])} \right) [\mathrm{dB}], \tag{VII.16}$$

where E denotes energy computed as

$$E(s[n]) = \sum_{n=0}^{N-1} s[n]^2, \tag{VII.17}$$

for s being a substitution for $x_c[n]$ and $x_r[n]$.

Next, absolute value of the first order derivative of $E(x_r[n])$ is computed as $E_d(x_r[n]) = |E'(x_r[n])|$. To quantify the variability of $E_d(x_r[n])$, a slope of its cumulative sum is computed as

$$E_\Delta = \Delta C(E_d), \tag{VII.18}$$

where $C(E_d)[n]$ for $n = 0, 1, \ldots, N-1$ refers to the cumulative sum applied on E_d, and Δ denotes the slope of a function. Finally, to compute the number of significant changes in $E_d(x_r[n])$, the number of its peaks E_p above the median value is computed.

Naming convention for TQWT-based features can be described as: FN, where F represents the name of the handwriting feature and N stands for the specific TQWT feature: signal-to-noise ratio (SNR), E_Δ as RES (csum), and E_p as RES (npeaks).

VII.2.3 Statistical analysis

At first, the features with any missing values were discarded from the analysis. Consequently, normality of the features was tested using Shapiro-Wilk test [63]. All non-normally distributed features were adjusted using Box-Cox [10] transformation. After the normalization, the features were re-inspected. As not all of the features were fully-normalized, an entire feature set was considered as being non-normally distributed. As a result, only non-parametric statistical methods were employed during the subsequent statistical analysis. Next, to control for the effect of confounding factors (also known as covariates), we computed the Spearman's correlation between the values of the features and the following characteristics: age, gender, grade (these characteristics were chosen after the consultation with psychologists and special educational counsellors). With this approach, age and grade were identified as having a statistically significant effect on the feature values. The effect of children's gender on the features was only marginal. Therefore, during the statistical analysis, we controlled for the effect of age and grade only. After the feature-transformation, we reduced the size of the feature set using a feature pre-selection process independently for each analyzed feature-type. More specifically, we used a filter method named minimum Redundancy Maximum Relevance (mRMR) to select a relevant sub-set of the features with minimum redundancy and cross-correlation among the features. After the feature pre-selection, we obtained 15 features per feature-type. Having the same number of the features for each features-type is important especially for the classification analysis, where each classifier is built starting with the same feature-space complexity.

Next, to compare the distribution of the graphomotor features for healthy children and children with GD, we used Mann-Whitney U-test with the significance level of 0.05. Moreover, to assess the strength of a relationship between the features and the children's clinical status (HC/GD), we computed Spearman's correlation coefficient with the significance level of 0.05. To control for the issue of multiple comparisons, p-values were adjusted using the False Discovery Rate (FDR) method.

Subsequently, to identify the presence of GD, we built binary classification models using an ensemble learning algorithm named Random Forests (RF) [11]. This particular algorithm was chosen due to its robustness to outliers, ability to find complex interactions among features as well as the possibility of ranking their importance. Using a randomized search strategy, we selected the following model settings: number of estimators (500), maximum tree depth (10), minimum number of samples required for splitting (2), minimum number of samples at a leaf node (1). Additionally, to train the models using only a parsimonious, information-rich sub-set of the features, to considerably decrease the risk of overfitting, and to reduce the computational performance requirements, we employed a feature selection process using a wrapper method named Sequential Floating Forward Selection (SFFS). As shown previously, reduction of the feature space complexity can significantly improve the model's prediction power [23].

To quantify the classification performance of the trained models as well as to control the addition and removal of the features during the feature selection, we used Matthew's correlation coefficient (MCC) [32]. This particular metric was chosen due to its ability to summarize the confusion matrix with the focus on obtaining a balance between the model's sensitivity and specificity [25]. The training and testing features were standardized before classification on a per-feature basis to have 0 mean and a standard deviation of 1. The trained models were evaluated conducting a stratified 5-fold cross-validation (we chose the 5-fold cross-validation scheme as a reasonable compromise between the number of samples in the training and validation folds) with 20 repetitions, and the classification test performance was determined using the following classification metrics: MCC, accuracy (ACC), sensitivity (SEN), and specificity (SPE).

Finally, to evaluate the statistical significance of the prediction performance obtained by the trained classification models, a non-parametric statistical method named permutation test was employed (exact p-values were computed to mitigate the type I error rate and the multiple testing issues) [45, 16]. In this work, we used

1 000 permutations and the significance level of 0.01 (to estimate the performance of the models on the permuted data, we used the same classification setup as in the training phase [42]).

VII.3 Results

At first, the cross-correlation matrices (using Pearson's correlation) of the 15 features per feature-type selected using feature pre-selection performed by the mRMR algorithm are visualized in Fig. VII.4. As can be seen, there are some features that can be considered redundant, i. e. having a strong correlation with one/more features, however, as we did not want to reduce the feature-space complexity too much (the redundancy is not the same in every feature-type, so by reducing the feature space complexity any further, some relevant features could be removed as well, which would most likely result in having sub-optimal feature space for some of the feature-types), we decided to use all of the 15 features, and analyze them accordingly (having the possibility of cross-correlated features appearing in the results of the statistical analysis together in mind).

Results of the statistical analysis can be seen in Table VII.2. The table shows the top 5 features for each of the feature-types according to the p-value computed by the Mann-Whitney U-test (if some of the cross-correlated features appeared together, we selected only one of them and replace the other with the feature/s bellow the top 5). Regarding the p-values of the Mann-Whitney U-test, the following number of features can be considered as coming from a distribution that is significantly different for the two subject groups (threshold of 0.05): a) CONV features – 5/5 (prior adjustment), 1/5 (after adjustment); b) MS features – 5/5 (prior adjustment), 4/5 (after adjustment); c) FD features – 5/5 (prior adjustment), 1/5 (after adjustment); and d) TQWT features – 3/5 (prior adjustment), 1/5 (after adjustment). With respect to the Spearman's correlation, the following features were found to have the strongest correlation with the presence of GD (where $**$ denotes p-value < 0.01, and $*$ denotes p-value < 0.05): a) CONV features – TSK1 TILT (mean) $\rho = -0.42^{**}$; b) MS features – TSK2 V-JERKR25 $\rho = 0.41^{**}$; c) FD features – TSK1 TILTVEL0.3 (mean) $\rho = -0.41^{**}$; and d) TQWT features – TSK6 V-VELSNR $\rho = -0.39^{**}$. All of these features were found to have a statistically significant relationship with the presence of GD (both prior and after p-value adjustment). For better visualization, violin plots showing the distribution estimates of the best-discriminating features of every feature-type for both healthy children and children with GD are presented in Fig. VII.5.

And finally, results of the classification analysis can be seen in Table VII.3.

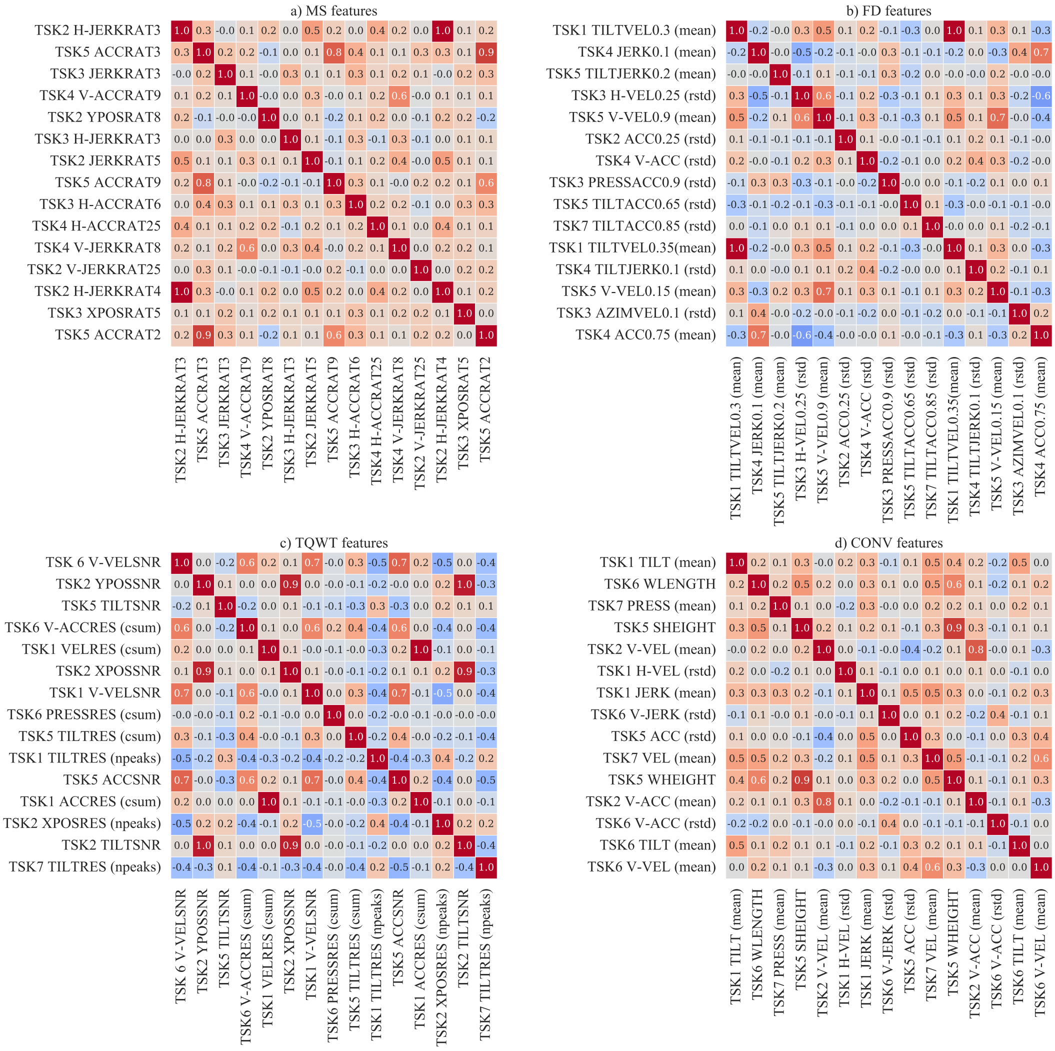

Fig. VII.4: Cross-correlation matrices of the feature sets (Pearson's correlation coefficient (r); 15 features per feature-type) after the pre-selection. Color notation: linear scale in the range of $< -1, 1 >$, where the maximum positive correlation is denoted by the red color, and the maximum negative correlation is denoted by the blue color. More information about the features can be seen in Section VII.2.2.

Regarding the individual feature-types, the following results were achieved (where $**$ denotes p-value < 0.01, and $*$ denotes p-value < 0.05): a) CONV features (7 features selected) – ACC $= 0.74^{**}$; b) MS features (8 features selected) – ACC $= 0.73^{**}$; c) FD features (3 features selected) – ACC $= 0.76^{**}$; and d) TQWT features (2 features selected) – ACC $= 0.71^{**}$. Features used to train these classification models for each feature-type are summarized in Table VII.4. With respect to an overall feature set (all 60 features combined), the classification performance was: ACC $= 0.84^{**}$ using 10 features. All classification results were evaluated by the permutation test as being statistically significant.

Table VII.2: Results of the statistical analysis.

feat.	TSK	ρ	p(ρ)	p(ρ)*	p(U)	p(U)*
		CONV features				
TILT (mean)	TSK1	-0.42	0.001	0.027	0.001	0.019
TILT (mean)	TSK6	-0.32	0.017	0.129	0.009	0.072
SHEIGHT (mean)	TSK5	-0.31	0.028	0.142	0.015	0.076
WLENGTH	TSK6	-0.25	0.074	0.190	0.038	0.096
WHEIGHT	TSK5	-0.25	0.074	0.190	0.038	0.096
		MS features				
V-JERKR25	TSK2	0.41	0.002	0.024	0.001	0.016
XPOSR5	TSK3	0.40	0.003	0.024	0.002	0.016
ACCR3	TSK5	0.36	0.009	0.033	0.005	0.020
JERKR3	TSK3	0.36	0.009	0.033	0.005	0.020
H-ACCR25	TSK4	0.27	0.058	0.146	0.030	0.075
		FD features				
TILTVEL0.3 (mean)	TSK1	-0.41	0.002	0.031	0.001	0.020
H-VEL0.25 (cv)	TSK3	-0.32	0.021	0.094	0.011	0.050
V-VEL0.9 (mean)	TSK5	-0.31	0.028	0.094	0.015	0.050
ACC0.75 (mean)	TSK4	0.30	0.031	0.094	0.016	0.050
ACC0.25 (cv)	TSK2	-0.25	0.074	0.152	0.038	0.077
		TQWT features				
V-VELSNR	TSK6	-0.39	0.004	0.070	0.003	0.044
V-ACCRES (csum)	TSK6	-0.26	0.061	0.345	0.031	0.177
ACCSNR	TSK5	-0.26	0.069	0.345	0.035	0.177
TILTSNR	TSK2	-0.23	0.110	0.409	0.055	0.206
V-VELSNR	TSK1	-0.21	0.136	0.409	0.068	0.206

[1] feat – feature; TSK – graphomotor task; ρ – Spearman's correlation coefficient; p(ρ) – p-value of ρ; p(ρ)* – adjusted p(ρ); p(U) – p-value of Mann-Whitney U-test; p(U)* – adjusted p(U); for the feature naming convention, see Section VII.2.2.

VII.4 Discussion

In the search for novel and more robust graphomotor features that can be used to improve the quantification and identification of GD in school-aged children, we introduced three non-conventional advanced types of features, specifically, features based on modulation spectra, features based on fractional order derivatives, and features based on tunable Q-factor wavelet transform. As each feature-type pro-

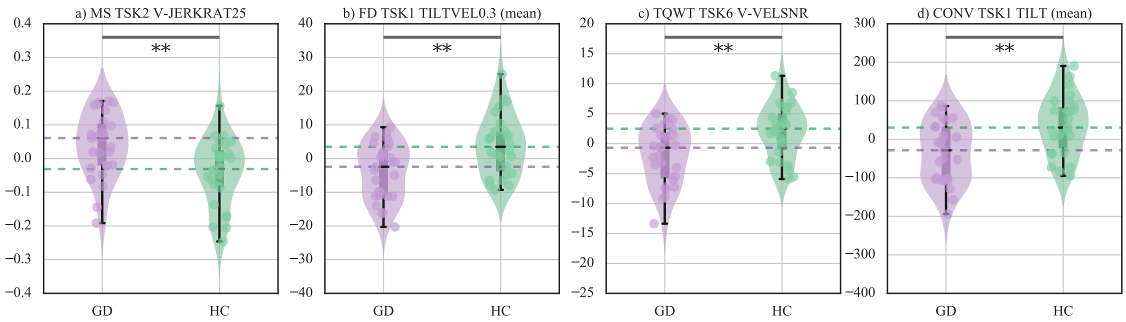

Fig. VII.5: Violin plots of graphomotor features in both GD and HC groups (after removing the covariates). Figure notation: background of the box plots represents vertically mirrored kernel density estimations; horizontal dashed lines represent medians; and a star(s) between two violins mean(s) the p-value of Mann-Whitney U-test ($**$ denotes p-value < 0.01, and $*$ denotes p-value < 0.05).

duced a different number of features, we employed feature pre-selection to reduce the feature-space complexity and minimize the effect of the curse of dimensionality occurring when the number of analyzed features greatly outnumbers the number of observations present in the dataset, as well as to unify the number of features among the feature sub-sets. With this approach, we reduced each feature-type to 15 features with minimal cross-correlation. An important observation to note here is that in all cases, the selected features do not cover an entire spectrum of the graphomotor tasks (TSK1–TSK7) under investigation. Moreover, the distributions of the tasks per feature-type vary as well. This indicates that each individual type of the features can potentially be used to describe slightly different task-specific as-

Table VII.3: Results of the classification analysis.

type	MCC	ACC	SEN	SPE	N	p
CONV	0.50 (0.26)	0.74 (0.12)	0.80 (0.19)	0.71 (0.21)	7	**
MS	0.48 (0.27)	0.73 (0.14)	0.75 (0.19)	0.73 (0.21)	8	**
FD	0.51 (0.30)	0.76 (0.13)	0.75 (0.20)	0.77 (0.20)	3	**
TQWT	0.42 (0.29)	0.71 (0.14)	0.74 (0.19)	0.68 (0.23)	2	**
ALL	0.65 (0.25)	0.84 (0.13)	0.83 (0.17)	0.81 (0.18)	10	**

[1] type – specific type of graphomotor feature; MCC – Matthew's correlation coefficient; ACC – accuracy; SEN – sensitivity; SPE – specificity; N – Number of selected features; p – p-values computed by the permutation test (1 000 permutations); ALL (combination of all feature-types, i. e. 60 features); for the feature naming convention, see Section VII.2.2.

Table VII.4: Features selected for the trained classification models.

CONV	MS	FD
TS6 V-ACC (cv)	TS5 ACCR2	TS3 H-VEL0.25 (cv)
TS1 H-VEL (cv)	TS3 H-ACCR6	TS7 TILTACC0.85 (cv)
TS7 VEL (mean)	TS2 YPOSR8	TS5 V-VEL0.9 (mean)
TS2 V-ACC (mean)	TS4 V-JERKR8	
TS1 TILT (mean)	TS2 JERKR5	
TS5 WHEIGHT	TS3 JERKR3	
TS2 JERK (mean)	TS2 V-JERKR25	
	TS5 ACCR3	
TQWT	**ALL**	
TS2 YPOSSNR	TSK1 H-VEL (cv)	
TS1 VELRES (csum)	TSK1 TILTVEL0.35 (mean)	
	TSK2 JERKR5	
	TSK3 JERKR3	
	TSK2 V-VEL (mean)	
	TSK6 V-ACC (cv)	
	TSK1 V-VELSNR	
	TSK3 PRESSACC0.1 (cv)	
	TSK7 TILTACC0.85 (cv)	
	TSK5 TILTRES (csum)	

[1] TSK – graphomotor task. For the feature naming convention, see Section VII.2.2.

pects of GD experienced by school-aged children supporting the use of a variety of specialized feature-types to provide a more robust and wide-scale description of the hidden complexities underlying GD in general.

Regarding the results of the statistical analysis, it can be seen that basic parameters such as mean tilt, height, and length of writing were found as the most statistically significant features in the case of the conventional (baseline) feature set. More specifically, mean tilt during the drawing of Archimedean spiral (TSK1) and rainbow (TSK6) showed the strongest relationship with the presence of GD. As can be seen, children with GD held the pen less steeply when performing such spiral- and rainbow shape-based movements. In addition, when compared with the cohort of healthy children, sawtooth (TSK5) and rainbow (TSK6) drawn by children with GD were found to be smaller in both height as well as length further underlining the difficulties associated with these tasks.

Another fact that can be observed in the results of the statistical analysis is that as opposed to the conventional features which consisted solely of the spatial (stroke length and height) and dynamic (tilt) parameters, the top-ranking non-conventional features mostly consisted of kinematic features (velocity, acceleration, and jerk) computed in both horizontal as well as vertical projections, and dynamic features (tilt). This observation is in line with the analysis performed by a variety of previous studies [27, 1, 12, 56] using kinematic features to quantify GD, and confirms the fact that kinematic features are an important measure of the quality of handwriting as well as drawing. Furthermore, such features are specific to computerized analysis as they are almost impossible to be quantified precisely using the human perception of the final handwritten product.

With respect to the features based on modulation spectra, all of the top-ranking features showed a positive correlation with the presence of GD indicating the existence of an increased low-frequency noise in the analyzed handwriting signals. This noise seems to be relatively task-independent as it appeared in all spiral-, loop- as well as sawtooth-based movements. Moreover, in four out of five cases, the features were based on acceleration or jerk, which points out to inability of children with GD to perform a given graphomotor task with steady and controlled velocity that is eventually reflected in an increased noise in the acquired kinematic signals (mathematical point of view) as well as in the lack of fluency and efficiency during handwriting (clinical point of view). Such observation is in line with the previous research reporting non-fluent handwriting as being present in children with HD (diagnosed with DD) [17, 35].

Regarding the top-ranking FD-based features, it may be noticed that all of them were extracted from different graphomotor tasks (TSK1–TSK5) further underlying the need for a variety of specifically-designed features to quantify GD. The most significant FD-based feature, the mean velocity of tilt extracted from TSK1, probably refers to the difficulties in changing the direction of the Archimedean spiral caused by hesitancy, distress, etc. This is an interesting finding as it is in line with the most significant conventional feature being the mean tilt, which highlights the importance of different tilt parametrizations. The rest of the most correlated FD-based features are derived from velocity and acceleration. This shows that FDs can be advantageously applied to both kinematic as well as dynamic features. Additionally, the values of α suggest that regular derivation is not optimal for kinematic handwriting features, which is in line with our previous research [39, 38].

Regarding the top-ranking TQWT features, the only statistically significant correlation was found for the signal-to-noise ratio of the vertical velocity extracted from the rainbow task (TSK6). This probably shows that maintaining steady velocity while performing this particular task is not causing problems to healthy children, but is challenging for children with GD, which is in line with the previous publication reporting problems in vertical movements in children with DD [27] caused by the psychological and muscular fatigue in the finger system. The vertical movement requires coordinated movement and finer flexions/extensions of more joints (interphalangeal and metacarpophalangeal) and therefore it is more complex than ulnar abductions of the wrist [18, 67], which plays a key role in the horizontal one, i. e. GD are more pronounced in the vertical projection of handwriting/drawing. Next, we assume, that children with GD are unable to quickly change the acceleration of their handwriting. On the other hand, healthy children have fewer problems with handwriting automation and therefore can change the acceleration more fluently. This can indirectly cause higher noise-level in the residual component of vertical acceleration in the handwritten product of healthy children, as can be seen in the second most significant TQWT feature.

Finally, concerning the results of the classification analysis, it can be seen that all of the three novel feature-types achieved similar classification performance in comparison to the conventional handwriting features. This shows that a single type of feature, even if more complex, is not likely to improve the identification of GD provided by the conventional features significantly. However, as the results suggest, when these features are combined, the classification performance can be increased by approximately 10 % in terms of accuracy, 3 % in terms of sensitivity and 10 % in terms of specificity. An important fact to note is that when compared with the previous research, the results proposed in this work might at first seem unsatisfactory as some of the recent publications reported over 90 % sensitivity [35, 49, 7]. However, those studies aimed at identifying HD in children with DD using a complex acquisition protocol comprising writing. The results proposed in this work are based solely on graphomotorics and aim at predicting the presence of GD that can lead to HD and possibly to DD. It is of great importance to also focus on simple graphomotor movements as they form the basis of handwriting, hence, a robust parametrization of GD has a potential to be used as an early marker of DD in children in pre-school age or first grades of a primary school. Another important fact to note is that all of the feature-types, as well as the conventional features, were selected when training the combined model. In addition, except TSK4 (flipped version of the connected loops in TSK3), all of the graphomotor tasks are present as well, This shows that all of the selected features extracted from almost all of the graphomotor tasks contributed to an improvement in the identification of GD confirming the hypothesis of enhancing the model's capability to model the relationship between the properties of the handwriting signals and the presence of GD in school-aged children.

VII.5 Limitations of the Study

This work has several limitations. First, we need to be aware of the restricted statistical strength of the inference about the population of school-aged children given a relatively small sample size of 53 children. Next, only children attending 3rd and 4th grade of the primary school were enrolled in this study. To obtain a more complex spectrum of handwriting signals, i. e. to have additional information about the performance of the proposed graphomotor features and their relationship with children's age, grade, etc., handwriting signals of children attending 1st and 2nd grade of the primary school (possibly even pre-school children) as well as children attending the higher grades should also be analyzed. On the other hand, our cohort includes children from the 3rd and 4th grade of primary schools, where the handwriting should become automatic. Therefore a possibility to identify GD in this stage is critical for the consequent diagnosis and therapeutic care of DD. The results proposed in this work therefore laid the foundations (baseline) for future studies that should bring even more information about GD in various age profiles and their evolution in time. Next, deeper investigation and design of the features can be performed, e. g. additional tuning of the filter-banks to compute modulation spectra, other formulations of fractional order derivatives or sub-bands of the tunable Q-factor wavelet transform could be analyzed. Next, various machine learning models should be trained and compared in the future studies to get more information about the classification performance of the proposed features and to obtain the most robust models for GD identification. Finally, the relationship between the classification performance of the trained models with the feature space complexity as well as the cross-validation setup should be investigated to evaluate and confirm the robustness of the proposed methodology. To sum up, concerning the limitations mentioned above, this study should be considered as being rather exploratory and pilot in nature, and its results should be confirmed by the subsequent scientific research.

VII.6 Conclusion

In this study, we presented three novel types of graphomotor features providing more robust and complex quantification of GD in school-aged children. In each feature-type, we identified several features that significantly differentiate healthy children and children with GD. Of note is the fact that the novel features mostly quantified kinematic aspects of the handwriting process that are very hard to be perceived by a human examiner using only a final handwritten product. In addition, we also showed that combining the proposed graphomotor features with the set of conventionally used ones can increase the prediction capability of the trained binary classifier significantly. With respect to the acquisition protocol, all of the chosen graphomotor tasks but one appeared in the final selection of the features used to train the combined classification model. This confirms that using a variety of basic graphomotor tasks requires coordinated movement of fingers, wrist, elbow, shoulder as well as visuospatial cognitive functions that allow the more advanced features to quantify subtle and rather imperceptible manifestations of GD using online handwriting.

To the best of our knowledge, it is the first work exploring the possibilities of using modulation spectra, fractional order derivatives and tunable Q-factor wavelet transform to extract advanced graphomotor features for the purpose of quantification and identification of GD in school-aged children. Based on the reported results, we conclude that the proposed features have a great potential to improve the computerized identification and assessment of GD. However, to generalize the results, our findings should be confirmed by further scientific research.

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VIII Analysis of Various Fractional Order Derivatives Approaches in Assessment of Graphomotor Difficulties

Outline

Bibliographic Information

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Author's Contribution

The author surveyed related works, proposed a new methodology extensions, designed and performed the analysis, and wrote a significant part of the manuscript. He was also working on the finalization of the whole manuscript, i.e. reviewing, copy-editing, etc.

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Abstract

Graphomotor disabilities (GD) are present in up to 30 % of school-aged children and are associated with several symptoms in the field of kinematics. Although the basic kinematic features such as velocity, acceleration, and jerk were proved to effectively quantify these symptoms, a recent body of research identified that the theory of fractional calculus can be used to even improve the objective GD assessment. The goal of this study is to extend the current knowledge in this field and explore the abilities of several fractional order derivatives (FD) approximations to estimate the severity of GD in the children population. We enrolled 85 children attending the 3rd and 4th grade of primary school, who performed a combined loop task on a digitizing tablet. Their performance was rated by psychologists and the online handwriting signals were parametrised by kinematic features utilising three FD approximations: Grünwald-Letnikov's, Riemann–Liouville's, and Caputo's. In this study, we showed the differences across the employed FD approaches for the same kinematic handwriting features and their potential in GD analysis. The results suggest that the Riemann-Liouville's approximation in the field of quantitative GD analysis outperforms the other ones. Using this approach, we were able to estimate the overall score with a low error of 0.65 points, while the scale range is 4. In fact, the psychologists tend to make the error even higher.

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VIII.1 Introduction

Fractional calculus (FC) is a name of the theory of integrals and derivatives of an arbitrary order [26]. The concept of fractional operators has been introduced almost simultaneously with the development of the classical differential, integral or other well-known calculus [14]. It attracted the interest of many famous mathematicians, including Euler, Liouville, Laplace, Riemann, Grünwald, and Letnikov. The principles of FC have been used in modeling of many physical and chemical processes, as well as in modern engineering and science in general [15, 30, 34]. It has been advantageously used during the modeling of different diseases such as the human immunodeficiency virus (HIV) [2] or malaria [25]. Recently, the FC has been significantly examined in computer vision, particularly in image restoration, super-resolution, image segmentation or motion estimation [33]. In line with this trend, in our recent research, we developed new parametrisation techniques of online handwriting (a handwritten signal with temporal information) based on the application of the fractional order derivative (FD) [22, 20, 21, 19].

It has been estimated that approximately 10–30 % of children experience graphomotor difficulties [1] such as graphomotor production deficits, motor feedback difficulties (e. g. the pen's tip location tracking problems), motor-memory dysfunctions, etc. Considering that children spend 31–60 % of their school-time performing handwriting [16], the early identification of graphomotor disabilities (GD) is crucial in the prevention of serious pedagogical and psychological consequences [12]. Otherwise, a child's every-day life can be greatly affected starting with a lack of motivation to write, a decrease in self-esteem in combination with poor emotional well-being continuing to bad attitude and behaviour, communication and social interaction problems [9]. In some cases, it may result in being diagnosed with a serious neurodevelopmental disorder such as developmental dysgraphia (DD) [24, 32]. To identify and evaluate GD in school-aged children, several well-established questionnaires or tests based on a visual inspection of the handwritten product have been developed [27, 29]. Though, their utilization on a day-to-day basis is still limited due to the fact that the administration and coding are very time-consuming. Furthermore, the perceptual abilities, experience, and subjective judgment of an examiner are limited as well.

To overcome the limitations of the perceptual GD analysis, researchers have been focusing on computerized quantitative analysis of online handwriting. Pen and paper have been replaced by digitizing tablets used to record a variety of signals describing the evolution of the handwritten product in time. It allowed quantification of kinematic (velocity, acceleration or jerk) as well as dynamic (pen pressure, tilt or azimuth) components of the handwritten signal. For instance, Pagliarini et. al. [23]

(2017) presented the potential of quantitative analysis to indicate the development of HD at a very early age. Mekyska et. al. [17] (2017) built a classifier (random forests, 27 children) identifying the presence of DD with 96 % sensitivity and specificity. Rosenblum and Dror [28] (2017) achieved 90 % sensitivity and specificity in DD classification (support vector machine, 99 children) using various kinematic and dynamic features. Asselborn et. al. [4] (2018) identify DD with 96 % sensitivity and 99 % specificity (random forests, 268 children) using 53 handwriting features. Next, Mekyska et. al. [18] (2019) built a classifier (XGBoost, 76 children) and achieved 50 % sensitivity and 90 % specificity in identification of GD presence using 7 basic graphomotor elements. Finally, Asselborn et. al. [3] (2020) reported four specific handwriting scores for kinematics, pressure, pen tilt and static features to describe the handwriting profile of a child. The overview of the mentioned current works and their achievemnts can be found in Table VIII.1

Considering the success of utilizing the FD (Grünwald-Letnikov approach) in Parkinson's disease dysgraphia analysis in our previous works [22, 20, 21, 19], and in the assessment of GD in school-aged children [39], this study, as a next logical step, has the following aims:

- to extend our previous research by the employment of several FD-approaches instead of one (Grünwald-Letnikov approach),
- to explore the differences of several FD approaches in the assessment of GD in the children population,
- to compare the power of the FD-based handwriting features computed by several FD approaches to estimate the severity of GD.

Table VIII.1: Overview of current works

Study	DB	Age	Tasks	Features	Results
Mekyska et al. [17] (2017)	27	8–9	Drawings	K, D, S, T, A	Classification: SEN = 98 %, SPE = 98 %; Regression: ERR = 10 %
Rosenblum et al. [28] (2017)	99	8–9	Writing	D, S, T	Classification: SEN = 90 %, SPE = 90 %
Asselborn et al. [4] (2018)	298	6–10	BHK tasks	K, D, S, A	Classification: SEN = 96 %, SPE = 99 %
Mekyska et al. [18] (2019)	76	6–11	Drawings	K, D, S, T	Classification: SEN = 50 %, SPE = 90 %
Galaz et al. [10] (2020)	53	9–12	Drawings	K, D, S, A	Classification: SEN = 83 %, SPE = 81 %
Asselborn et al. [3] (2020)	448	5–12	BHK tasks	K, D, S, T	New data-driven based approaches for an assessment of GD (4 dimensions)
Garot et al. [11] (2020)	280	5–12	BHK tasks	K, D, S, T	Automatic discrimination among 3 groups of children with dysgraphia

[1] DB – database size; BHK – Concise Evaluation Scale for Children's Handwriting; D – dynamic handwriting features; K – kinematic handwriting features; S – spatial handwriting features; T – temporal handwriting features; A – advanced handwriting features; SEN – sensitivity; SPE – specificity; EER – estimation error rate; GD – graphomotor disabilities

VIII.2 Dataset & Methodology

VIII.2.1 Dataset

For this study, we enrolled 85 children (31 girls and 54 boys) attending 3rd and 4th grade at several primary schools in the Czech Republic. The demographic data of the participants can be found in Table VIII.2 and the resulting grade distribution in Table VIII.3. Children were asked to perform drawings, writings, and several cognitive tests based on a protocol consisting of 31 tasks designed in cooperation with psychologists and special educational counselors. Every graphomotor task of the protocol has been evaluated by a well-experienced psychologist and rated on the scale from 0 to 4 where: 0 – no graphomotor difficulties; 1 – mild graphomotor difficulties; 2 – graphomotor difficulties; 3 – dysgraphia; 4 – severe dysgraphia. Finally, an overall score has been assigned to each child based on a complex analysis of all the 31 tasks in the protocol (i.e. including the cognitive tests). Although the protocol contains 7 graphomotor tasks such as Archimedean spiral, loops, sawtooth, or rainbow, in this study, we focused on one graphomotor task (combined loops), which has been proved to discriminate well between children with/without graphomotor difficulties [18]. The distribution of scores (the overall and the sub-score for the combined loops task) is presented in Fig. VIII.1. Correlation between the scores and the demographic data is visualized in Fig. VIII.2. Parents of all children participating in this study signed an informed consent form approved by the Ethical Committee of the Masaryk University. Throughout the entire duration of this study, we strictly followed the Ethical Principles of Psychologists and Code of Conduct released by the American Psychological Association (https://www.apa.org/ethics/code/).

VIII.2.2 Data Acquisition

At first, a template of the combined loop task was shown to a child and then he/she was asked to replicate it on an A4 paper that was laid down and fixed to a digitizing tablet. The drawing was acquired by the Wacom Intuos Pro L (PHT-80) digitizer with the sampling frequency of 150 Hz, and the Wacom Inking pen, which provides a feeling of writing by a regular pen and offers immediate visual feedback. Moreover, this set-up enabled us to record a variety of signals describing the drawing process: x and y position ($x[n]$ and $y[n]$); timestamp ($t[n]$); a binary variable ($b[n]$; 0 – in-air movement, i. e. movement of the pen tip up to 1.5 cm above the tablet's surface, and 1 – on-surface movement, i. e. movement of the pen tip on the paper), pressure exerted on the tablet's surface during drawing ($p[n]$); pen tilt ($a[n]$); and azimuth ($az[n]$). For more information, see our previous works [17, 19, 39]. An example of

Table VIII.2: Demographic data of the enrolled children.

	μ (σ)	min	Q1	Q2	Q3	max
all children (85 subjects)						
age [y]	9.79 (0.65)	8	9	10	10	11
class	3.86 (0.35)	3	4	4	4	4
sub-score	1.46 (0.82)	0	1	1	2	3
overall score	1.75 (0.84)	0	1	2	2	4
girls (31 subjects)						
age [y]	9.77 (0.66)	8	9	10	10	11
class	3.84 (0.37)	3	4	4	4	4
sub-score	1.16 (0.72)	0	1	1	2	2
overall score	1.35 (0.86)	0	1	1	2	3
boys (54 subjects)						
age [y]	9.80 (0.65)	8	9.25	10	10	11
class	3.87 (0.34)	3	4	4	4	4
sub-score	1.63 (0.82)	0	1	1	2	3
overall score	1.98 (0.73)	1	1.25	2	2	4

[1] μ – mean; σ – standard deviation; Qx – x-th quartile; y – years.

Table VIII.3: Grade distribution.

grade	girls	boys	together
3rd grade	5	7	12
4th grade	26	47	73

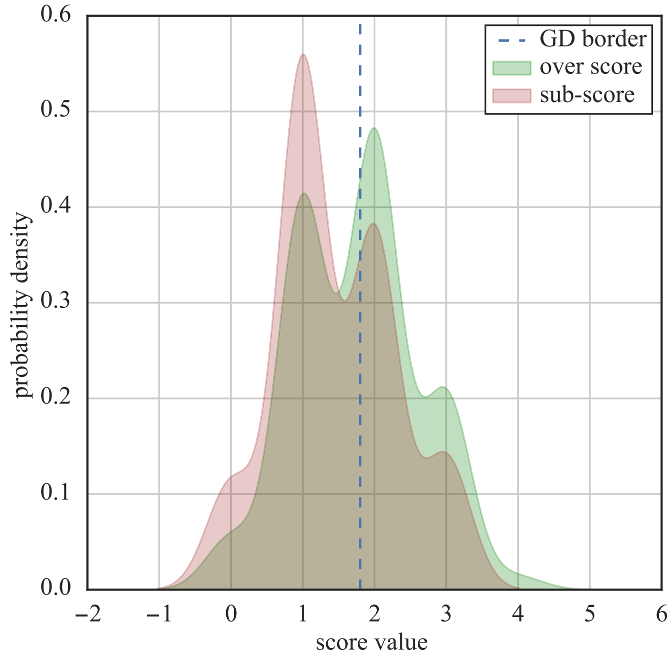

Fig. VIII.1: Distribution of the overall score and the sub-score (after standardization). Blue dashed line represents imaginary threshold for the graphomotor difficulties (right of the line).

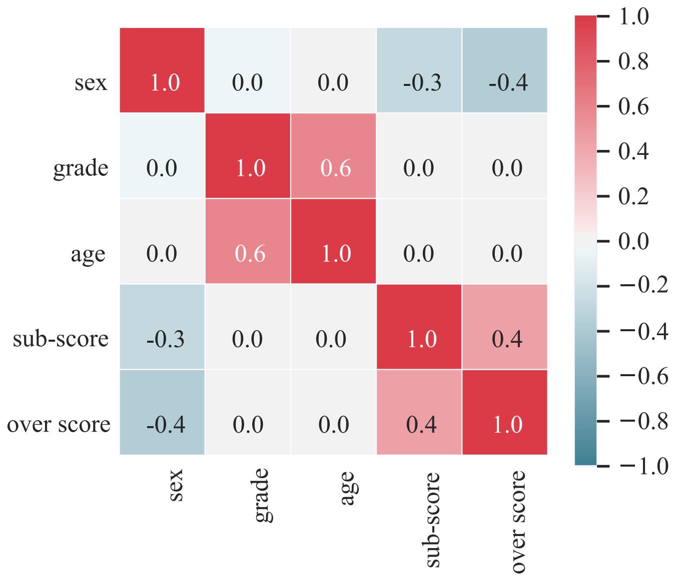

Fig. VIII.2: Correlation matrix between the scores and demographic data of the participants. A positive correlation is represented by red color and a negative correlation by blue color.

the selected combined loop task performed by a child with/without GD can be seen in Fig. VIII.3.

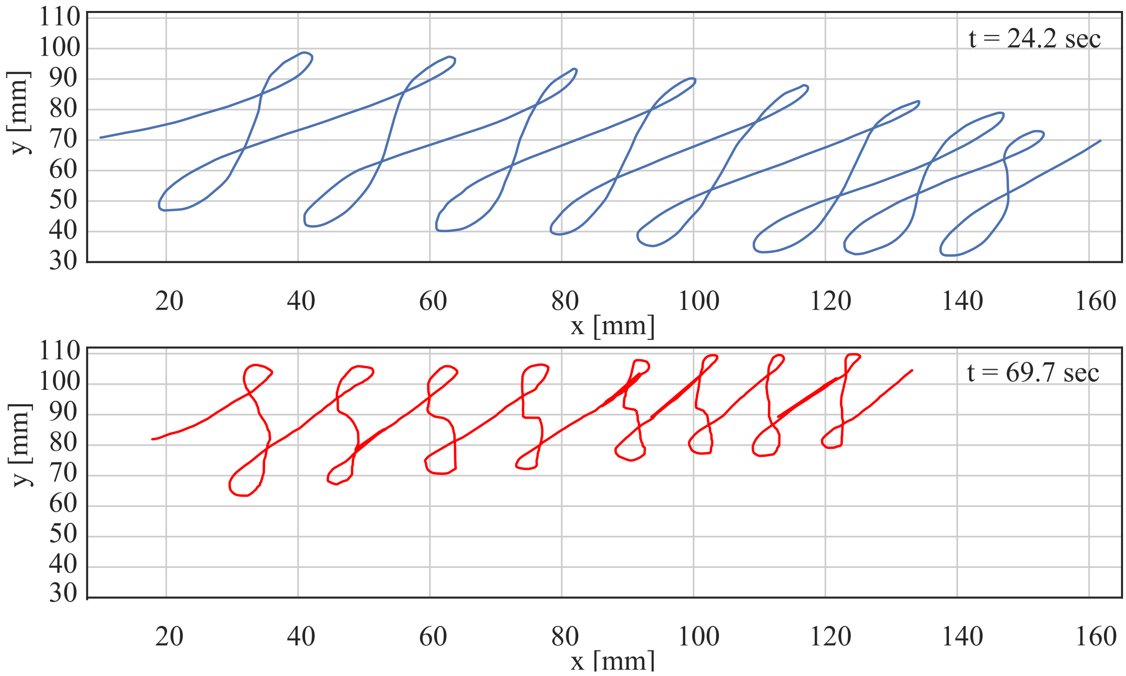

Fig. VIII.3: Example of the combined loop task performed by a child without graphomotor difficulties (upper part) and with graphomotor difficulties (bottom part). The thick parts of the red line represent the line-up places after the interruptions of the writing.

VIII.2.3 Fractional Order Derivatives

The essential of this study is the investigation of the several (non-equivalent) FD approximations as a new advanced approach of drawing/handwriting parameterisation. We developed this method to substitute the conventional differential derivative in the feature extraction process (see our previous works [19, 39, 22, 20, 21]) in order to improve the quantitative analysis of the GD. In the scope of this study, we utilized three FD approximations: Grünwald-Letnikov (GL), Riemann–Liouville (RL), and Caputo (C), implemented by Valério Duarte in Matlab [35, 36, 37].

VIII.2.3.1 Grünwald-Letnikov

The FD definition by Grünwald-Letnikov is one of the first and basic approaches [14]. A direct definition of of the derivation of the function $y(t)$ by the order $\alpha - D^{\alpha}y(t)$ [26] is based on the finite differences of an equidistant grid in $[0, \tau]$, assuming that the function $y(t)$ satisfies certain smoothness conditions in every finite interval

$(0,t), t \leq T$, where T denotes the period. Choosing the grid

$$0 = \tau_0 < \tau_1 < ... < \tau_{n+1} = t = (n+1)h \tag{VIII.1}$$

with

$$\tau_{k+1} - \tau_k = h \tag{VIII.2}$$

and using the notation of finite differences

$$\frac{1}{h^\alpha}\Delta_h^\alpha y(t) = \frac{1}{h^\alpha}\left(y(\tau_{n+1}) - \sum_{v=1}^{n+1} c_v^\alpha y(\tau_{n+1-v})\right), \tag{VIII.3}$$

where

$$c_v^\alpha = (-1)^{v-1}\tbinom{\alpha}{v}. \tag{VIII.4}$$

The Grünwald–Letnikov definition from 1867 is defined as

$$^{GL}\mathrm{D}^\alpha y(t) = \lim_{h\to 0}\frac{1}{h^\alpha}\Delta_h^\alpha y(t), \tag{VIII.5}$$

where $^{GL}\mathrm{D}^\alpha y(t)$ denotes the Grünwald-Letnikov derivative of order α of the function $y(t)$, and h represents the sampling lattice.

VIII.2.3.2 Riemann–Liouville

Another classical form of the FD has been given by Riemann-Liouville. The left-inverse interpretation of $D^\alpha y(t)$ by Riemann-Liouville [26, 15] from 1869 is defined as

$$^{RL}\mathrm{D}^\alpha y(t) = \frac{1}{\Gamma(n-\alpha)}\left(\frac{d}{dt}\right)^n \int_0^t (t-\tau)^{n-\alpha-1} y(t)dt, \tag{VIII.6}$$

where $^{RL}\mathrm{D}^\alpha y(t)$ denotes the Riemann–Liouville derivative of order α of the function $y(t)$, Γ is the gamma function and $n-1 < \alpha \leq n, n \in \mathbf{N}, t > 0$.

VIII.2.3.3 Caputo

Nowadays, the most significant contributions to the field of FC are the results achieved by M. Caputo [6]. In contrast to the previous ones, the improvement hereabouts lie in the unnecessity to define the initial FD condition [15, 26]. The Caputo's definition from 1967 is

$$^{C}\mathrm{D}^\alpha y(t) = \frac{1}{\Gamma(n-\alpha)}\int_0^t (t-\tau)^{n-\alpha-1} y^n(t)dt, \tag{VIII.7}$$

where $^{C}\mathrm{D}^\alpha y(t)$ denotes the Caputo derivative of order α of the function $y(t)$, Γ is the gamma function and $n-1 < \alpha \leq n, n \in \mathbf{N}, t > 0$.

VIII.2.4 Handwriting Features

Altogether, we extracted 3 sets of handwriting features, one feature set per one employed FD approach. Basic kinematic features from the input handwritten signal were extracted as well, namely velocity, acceleration, jerk and their horizontal and vertical variants. Due to rare omissions of 3–4 samples by the digitizing tablet during the acquisition, we performed the in-signal outliers removal (outliers were considered as elements more than three scaled median absolute deviations from the median). If not pre-processed, the differentiation of this gap would leave significant peaks in the output handwriting feature as illustrated in Figure VIII.4. All handwriting features were computed for α in the range of 0.1–1.0 (with 0.1 step), where $\alpha = 1.0$ is equal to the full derivation. Finally, the statistical properties of all extracted handwriting features were described by the mean and the relative standard deviation (relstd). To sum up, each feature set consists of 180 computed kinematic features.

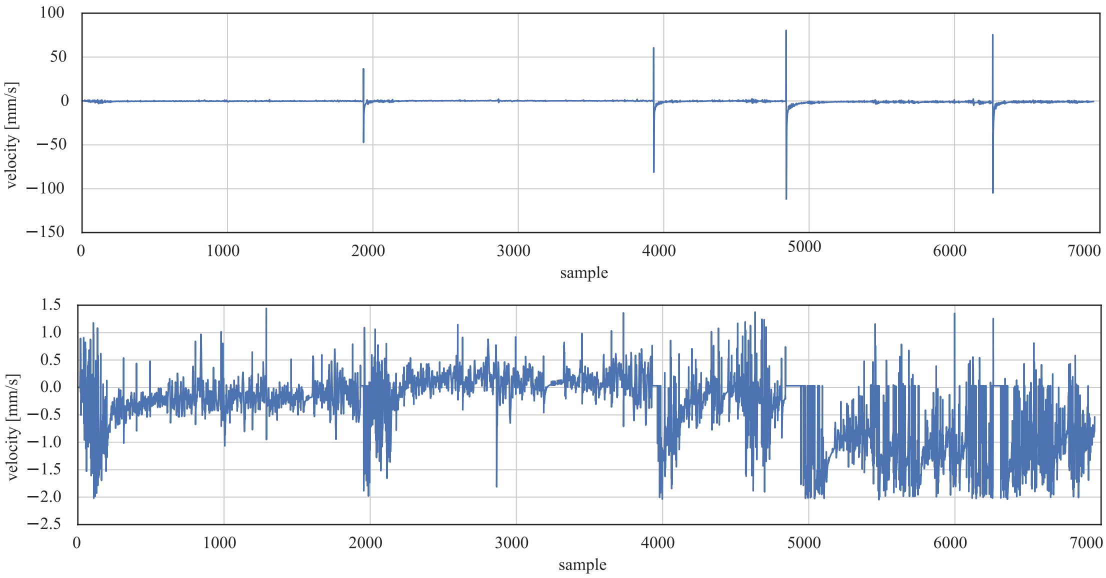

Fig. VIII.4: Illustration of the in-signal outlier removal, where the original handwritten signal before removing the outlier samples is placed in the upper part and after the outlier removal in the bottom part of the Figure. The velocity for $\alpha = 0.7$ computed by Caputo's approach from a sample of healthy children is used. The magnitude of the removed samples (peaks) is up to 100-times higher in comparison with the normal ones.

VIII.2.5 Statistical Analysis

At first, we performed the normality test of the handwriting features using the Shapiro-Wilk test [31]. In the case of non-normally distributed features, we utilised the Box-Cox transformation [5].

Next, to assess the strength of the relationship between the feature values and the scores (the overall score and the sub-score), Spearman's and Pearson's correlation coefficients were computed (we considered the level of significance 0.05). The p-values were adjusted using the False Discovery Rate (FDR) method to address the issue of multiple comparisons.

During the statistical analysis, we controlled for the effect of several confounding factors (covariates), namely age, grade, and sex.

Finally, to evaluate the power of the handwriting features to support the estimation of scores assessing the GD, we performed a multivariate analysis. For this purpose, we employed the state-of-the-art algorithm XGBoost [7] (10-fold cross-validation with 20 repetitions). The XGBoost algorithm was selected, because of its ability to achieve good performance on a small data set. Hyper-parameter space optimization was performed by a grid search strategy. The model's performance was evaluated by the mean absolute error (MAE), the mean square error (MSE), the root mean square error (RMSE), and the estimation error rate (EER).

VIII.3 Results

The results of the correlation analysis can be seen in Table VIII.4 and Table VIII.5. The table shows the top 5 features per FD approximation according to p-values of the Spearman's correlation related to the overall score (upper part) and the sub-score (bottom part). The strongest correlation (after the FDR adjustment) with the overall score was identified in features extracted by the Caputo's FD. However, in the case of the sub-score, the Riemann-Liouville's FD arises as the most significant.

The correlation matrices (using the Spearman's correlation) are visualized in Fig. VIII.5. Each matrix includes the top 5 features per FD approximation (i. e. 15 features in one matrix) identified in Table VIII.4 and Table VIII.5. The distribution of the FD order α of 20 best features regarding the Spearman's correlation per FD approximation is visualised in Fig. VIII.6 for the overall score and in Fig. VIII.7 for the sub-score.

Finally, the results of the multivariate analysis can be found in Table VIII.6. In the case of the overall score estimation, the best results were achieved by the Riemann-Liouville FD. In the case of the sub-score estimation, the lowest error was achieved when combining features of all the approximations. Hyper-parameters of the best XGBoost models can be found in Table VIII.7

Table VIII.4: Results of the correlation analysis between the overall score values and computed handwriting features ranked by the adjusted p-value of Spearman's correlation.

	overall score					
feature name	ρ	p_s	p_s^*	r	p_p	p_p^*
			Caputo			
relstd jerk-α=0.4	**-0.3821**	**0.0003**	**0.0360**	**-0.1624**	**0.1377**	**0.5934**
relstd acceleration-α=0.3	-0.3649	0.0006	0.0360	-0.1204	0.2723	0.5934
relstd jerk-α=0.6	-0.3669	0.0006	0.0360	-0.1510	0.1678	0.5934
relstd jerk-α=0.8	0.3542	0.0009	0.0405	0.0702	0.5230	0.7298
relstd velocity-α=0.2	-0.3405	0.0014	0.0504	-0.1492	0.1729	0.5934
			Grünwald-Letnikov			
relstd velocity-α=0.9	-0.3435	0.0013	0.1106	0.0447	0.6843	0.9988
mean v. jerk-α=0.2	-0.3178	0.0030	0.1106	-0.0902	0.4118	0.9988
mean h. jerk-α=0.2	0.3113	0.0037	0.1106	0.2146	0.0486	0.6194
mean v. jerk-α=0.1	-0.3071	0.0043	0.1106	-0.0729	0.5071	0.9988
relstd v. jerk-α=0.1	-0.2811	0.0092	0.1998	-0.0180	0.8702	0.9988
			Riemann-Liouville			
relstd h. acceleration-α=0.9	0.3472	0.0011	0.0709	0.1304	0.2343	0.9521
relstd h. jerk-α=0.6	0.3154	0.0033	0.0709	0.0502	0.6481	0.9521
relstd velocity-α=0.4	-0.3144	0.0034	0.0709	0.0173	0.8753	0.9847
mean jerk-α=0.1	-0.3058	0.0044	0.0709	-0.0901	0.4122	0.9521
mean acceleration-α=0.6	-0.3047	0.0046	0.0709	-0.0880	0.4231	0.9521

[1] ρ – Spearman's correlation coefficient; p_s – p-value of Spearman's correlation; p_s^* – adjusted p-value of Spearman's correlation; r – Pearson's correlation coefficient; p_p – p-value of Pearson's correlation; p_p^* – adjusted p-value of Pearson's correlation; relstd – relative standard deviation; h. – horizontal; v. – vertical.

VIII.4 Discussion

The main goal of this study is to explore the differences across various FD approximations utilized in the analysis of the GD. A comparison of an identical feature (i. e. velocity for $\alpha = 0.2$) extracted from the handwritten product associated with the GD (the same sample as in the bottom part of Fig. VIII.3) is shown in Fig. VIII.8. It illustrates the differences across the involved FD approximations. The velocity function extracted by the Caputo's FD dominates by significant peaks in the positions, where a child interrupts the performance for a moment and then continues writing. These interruptions are also visible in the function computed by the

Table VIII.5: Results of the correlation analysis between the sub-score values and computed handwriting features ranked by the adjusted p-value of Spearman's correlation.

	sub-score					
feature name	ρ	p_s	p_s^*	r	p_p	p_p^*
			Caputo			
relstd acceleration-α=0.3	-0.3353	0.0017	0.1560	-0.1294	0.2380	0.6211
relstd h. jerk-α=0.8	-0.3319	0.0019	0.1560	-0.1918	0.0787	0.4047
relstd velocity-α=0.2	-0.3230	0.0026	0.1560	-0.1888	0.0835	0.4175
relstd velocity-α=0.3	-0.2904	0.0070	0.2556	-0.0406	0.7121	0.8720
relstd acceleration-α=0.1	-0.2898	0.0071	0.2556	0.0003	0.9975	0.9975
			Grünwald-Letnikov			
relstd velocity-α=0.1	0.3475	0.0011	0.1980	0.3231	0.0026	0.2603
relstd velocity-α=0.2	0.3196	0.0029	0.1980	0.2784	0.0099	0.2603
relstd velocity-α=0.7	0.3157	0.0033	0.1980	0.2247	0.0387	0.2603
relstd velocity-α=0.6	0.2923	0.0066	0.2970	0.1150	0.2945	0.5049
relstd jerk-α=0.5	-0.2781	0.0100	0.3600	-0.0979	0.3729	0.5888
			Riemann-Liouville			
relstd h. acceleration-α=0.9	**0.4014**	**0.0001**	**0.0180**	**0.1548**	**0.1571**	**0.6672**
mean h. acceleration-α=0.8	0.3767	0.0004	0.0360	0.0833	0.4484	0.8302
relstd h. velocity-α=0.8	0.3649	0.0006	0.0360	0.0030	0.9786	0.9850
mean h. acceleration-α=0.7	0.3539	0.0009	0.0405	0.0678	0.5375	0.8346
mean h. acceleration-α=0.9	0.3394	0.0015	0.0411	0.0952	0.3859	0.8302

[1] ρ – Spearman's correlation coefficient; p_s – p-value of Spearman's correlation; p_s^* – adjusted p-value of Spearman's correlation; r – Pearson's correlation coefficient; p_p – p-value of Pearson's correlation; p_p^* – adjusted p-value of Pearson's correlation; relstd – relative standard deviation; h. – horizontal; v. – vertical.

Riemann-Liouville approach, though in the form of a constant line followed by elevated oscillations instead of peaks. On the other hand, the function based on the Grünwald-Letnikov approach seems to be a constant line, nevertheless after a scale normalization (min-max normalization), see Fig. VIII.9, it is clear that the function has the oscillatory nature as well.

The differences across FD approaches are underlined by the comparison in Fig. VIII.10, where the dependency of the relative standard deviation of the velocity on the FD order α is visualized. Feature values computed by the Grünwald-Letnikov approach are generally higher in comparison with the Caputo and Riemann-Liouville ones, which are more similar. On the other hand, the envelope of the velocity profile

Table VIII.6: Results of the multivariate analysis.

		overall score (range 4)			
APP	MAE	MSE	RMSE	EER [%]	N
GL	0.72 ± 0.17	0.76 ± 0.30	0.85 ± 0.18	17.93 ± 4.30	5
C	0.76 ± 0.21	0.95 ± 0.45	0.95 ± 0.24	19.01 ± 5.07	24
RL	**0.65 ± 0.16**	**0.66 ± 0.28**	**0.79 ± 0.17**	**16.25 ± 3.96**	**16**
ALL	0.68 ± 0.18	0.73 ± 0.33	0.83 ± 0.20	17.09 ± 4.50	17
		sub-score (range 3)			
APP	MAE	MSE	RMSE	EER [%]	N
GL	0.68 ± 0.16	0.70 ± 0.29	0.82 ± 0.17	22.53 ± 5.23	18
C	0.65 ± 0.18	0.75 ± 0.33	0.85 ± 0.19	21.75 ± 6.10	15
RL	0.66 ± 0.15	0.66 ± 0.25	0.79 ± 0.16	22.03 ± 5.04	24
ALL	**0.64 ± 0.15**	**0.63 ± 0.24**	**0.78 ± 0.16**	**21.44 ± 5.02**	**17**

[1] APP – specific FD approximation; MAE – mean absolute error; MSE – mean squared error; RMSE – root mean squared error; EER – estimation error rate; N – number of selected features; GL – Grünwald-Letnikov; C – Caputo; RL – Riemann–Liouville; ALL (combination of all feature-types, i. e. 540 features).

Table VIII.7: Hyper-parameters of the best XGBoost models

hyper-parameter	overall score	sub-score
gamma	0.1	0.1
learning rate	0.1	0.1
maximum depth of a tree	15	8
minimum child weight	0.5	0.5
balance of positive and negative weights	1	1
sub-sample ratio	0.9	1
sub-sample ratio of columns for tree	0.9	0.5
sub-sample ratio of columns for level	0.9	0.4
number of estimators	500	500
seed	42	42

based on the Grünwald-Letnikov approach is more similar to the Riemann-Liouville one. Moreover, all functions meet at the point where $\alpha = 0.9$ and continue simultaneously to the full derivation ($\alpha = 1.0$), which is expected, because the full derivation has to be the same for all approaches.

Experts in the field of psychology need to understand and clearly interpret the results of the graphomotor analysis, i. e. to link them with specific symptoms or physiological processes. This is very challenging especially in the case of advanced signal parameterisation, which is also our case. Therefore, to bring credibility for a non-technical reader, we provide an illustration in Fig. VIII.11. In this figure, we compare the vertical projection of the movement (y axis) and the vertical velocity (Grünwald-Letnikov approach, $\alpha = 0.8$) in a child without graphomotor difficulties (same as in the upper part of Fig. VIII.3). The function extracted by FD for $\alpha = 0.8$ is difficult to be understood, but the relationship to the velocity is obvious.

Regarding the results of the correlation analysis (association with the overall score), the most significant features (after the FDR adjustment) are extracted by the Caputo's FD, where the top 5 have the p-value < 0.05. Most significant handwriting features are related to the variability of the jerk, which refers to the disturbances in the fluent handwriting performance of the child with GD. The values of the correlation coefficients are negative, which means that the handwriting performance of the subject is worse with the lower variability of the jerk. This may be confusing, because just the opposite effect may be expected. Nevertheless, this is specific for the combined loop task. A child without GD is less focused on the writing (the movement is more automatic), therefore the changes between loops are more dynamic, which results in higher jerk variability. Vice versa, a child with GD is more focused on his/her performance, therefore, the handwriting is associated with lower acceleration and jerk. In the case of Grünwald-Letnikov based features, 4 out of

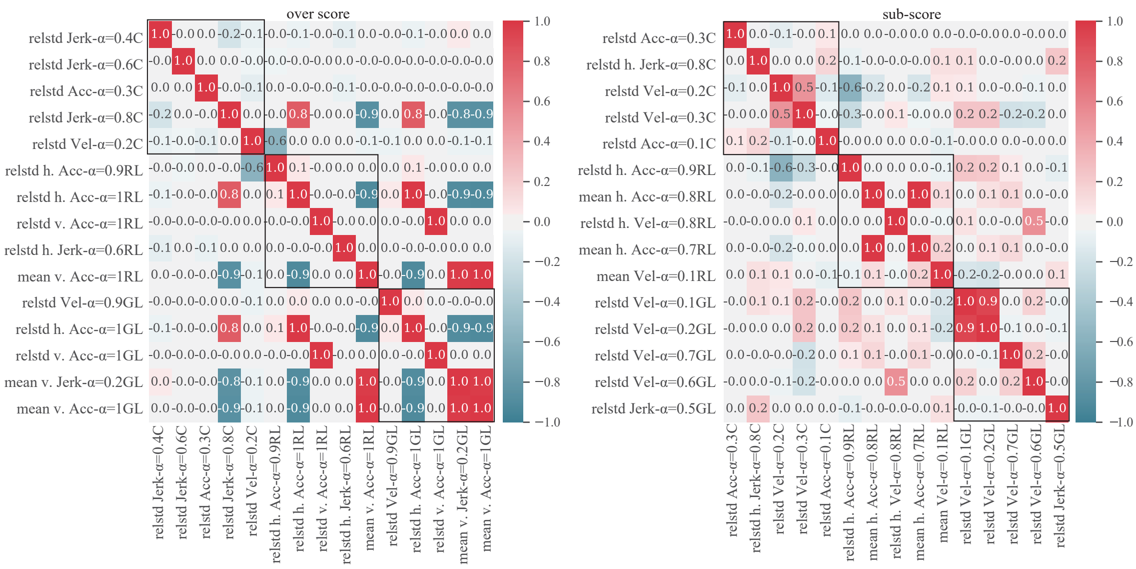

Fig. VIII.5: Cross-correlation matrices of the most significant FD features as assessed by the Spearman's correlation (see Table VIII.4, VIII.5). Framed sub-areas in each cross-correlation matrix visually isolates the handwriting features computed by the same FD approach.

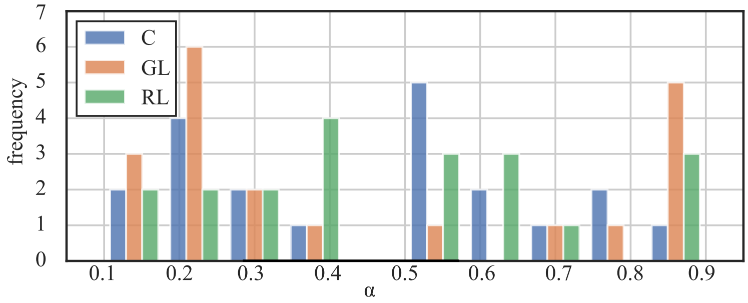

Fig. VIII.6: Distribution of the FD order α for the features mostly correlating with the **overall score**, see Table VIII.4 (GL – Grünwald-Letnikov; C – Caputo; RL – Riemann–Liouville).

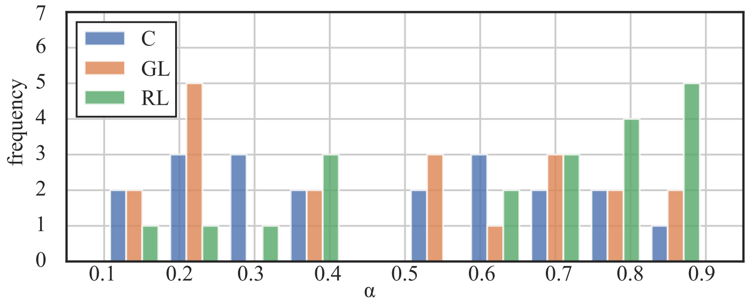

Fig. VIII.7: Distribution of the FD order α for the features mostly correlating with the **sub-score**, see Table VIII.5 (GL – Grünwald-Letnikov; C – Caputo; RL – Riemann–Liouville).

the 5 most significant ones are jerk related too, what supports the results obtained by the Caputo's approach. In the view of the Riemann-Liouville FD, the most significant features are mostly acceleration and jerk related, this likewise supports the association with the smooth handwriting disabilities.

Considering the correlation with the sub-score, the most significant features (after the FDR adjustment) are extracted by the Riemann-Liouville FD, while 4 out of 5 features are acceleration-based. This again refers to the disruptions in continuous handwriting of a child with GD (i. e. less automatic and dynamic movements). In the case of the Grünwald-Letnikov approach, the variation of the velocity is observed to be the most significant, however, none of the features is significant after the p-value adjustment (similarly to the Caputo's approach). Due to the omission of the full derivations in best correlation results, the FD-based features outperform the conventional handwriting features in the scope of the sub-score correlation analysis for the connected loops task. In addition, this is in line with our previous results. [19, 21].

Regarding the cross-correlation of the top-ranked features strongly associated

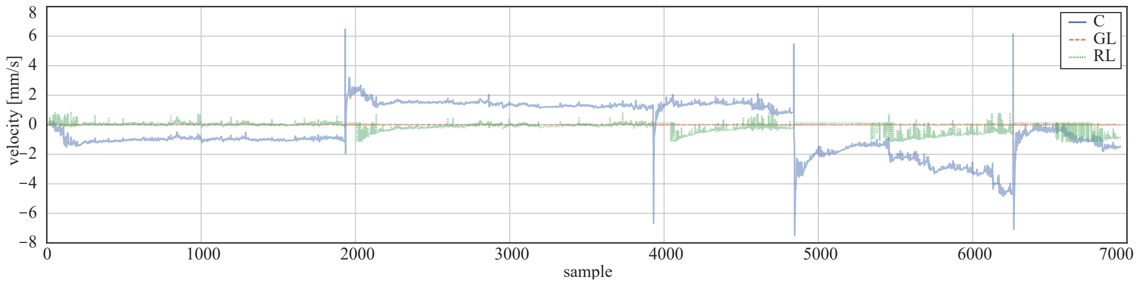

Fig. VIII.8: Comparison of the velocity function (α=0.2) across all the FD approximations (a child associated with graphomotor difficulties; C – Caputo; GL – Grünwald-Letnikov; RL – Riemann–Liouville).

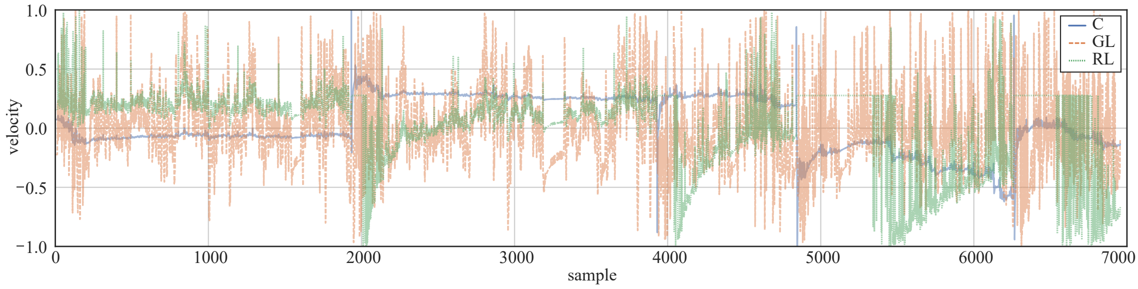

Fig. VIII.9: Comparison of the velocity function (α=0.2, normalized scale) across all the FD approximations (a child associated with graphomotor difficulties; C – Caputo; GL – Grünwald-Letnikov; RL – Riemann–Liouville).

with the overall score (see the left matrix in Fig. VIII.5), we did not observe any strong correlations among the features based on the Caputo's approach. In the case of the Riemann-Liouville's approximation, we identified a significant correlation between the mean of the vertical acceleration and the relstd of the horizontal acceleration, in both features $\alpha = 1$, which means full derivation. Similarly, in the Grünwald-Letnikov's approach, we identified a strong association between the relstd of the horizontal acceleration, and the mean vertical jerk and the mean vertical acceleration. The last two mentioned features are in fact very close to each other, because the acceleration with $\alpha = 1$ is very similar to the jerk with $\alpha = 0.2$.

We assume that the above-mentioned association is linked with the fact that the vertical movement, contrary to the horizontal one, requires coordinated movement and finer flexions/extensions of more joints (interphalangeal and metacarpophalangeal) and therefore, it is more complex than ulnar abductions of the wrist [8, 38]. Since the vertical movement is complex, it is strongly affected by psychological and muscular fatigue [13], which could be manifested in lower vertical acceleration in children with GD. Nevertheless, low relstd in the horizontal direction could mean monotonous and less dynamic movement too.

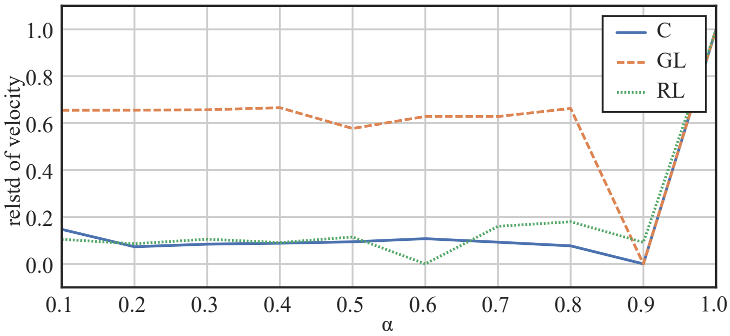

Fig. VIII.10: Relative standard deviation of velocity depending on FD order α (C – Caputo; GL – Grünwald-Letnikov; RL – Riemann–Liouville).

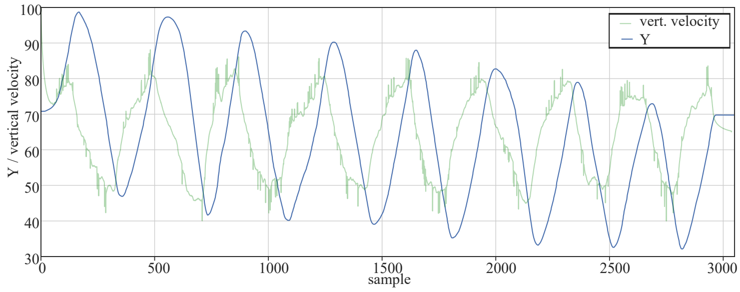

Fig. VIII.11: Comparison of the vertical projection of movement and the vertical velocity (Grünwald-Letnikov, $\alpha = 0.8$) in a child without graphomotor difficulties.

In the case of the cross-correlation matrix linked with the sub-score, we can observe significant correlations only in features that express the same information, e. g. the mean of the horizontal acceleration, but differ only in α, e. g. the difference is 0.1. Since this difference is very low, it is obvious that these features significantly correlate. Except for this, the features do not correlate much among themselves which means that they are not redundant, but still relevant (see Table VIII.4,VIII.5).

Based on the distribution of α in the 20 top-ranked features, we can observe that those based on the Caputo's approach are mostly concentrated around 0.2 and 0.5 for the overall score and almost evenly distributed in the case of sub-score correlation analysis. The Grünwald-Letnikov FD-based features associated with the overall score have α concentrated around 0.2 and 0.9. Those associated with the sub-score are mainly around 0.2, 0.5 and 0.7. Finally, in the case of the Riemann-Liouville's approach, we can observe a higher concentration in the range [0.4; 0.6] for the overall score, and in the range [0.7; 0.9] for the sub-score. Since the distribution of the α varies per FD approximation and rating scale, we hypothesise that further and finer optimization of this parameter would bring even better quantification of the GD.

Concerning the multivariate analysis (Table VIII.6), where we estimated the overall score, the best results were achieved by the Riemann-Liouville FD-based features. The resulting MAE was 0.65, and RMSE = 0.79. When estimating the sub-score, all approaches had a very similar MAE, nevertheless, the lowest RMSE (0.79) was reached by the Riemann-Liouville's approach too. A combination of all the approaches slightly decreased the error. These results suggest that the Riemann-Liouville's approximation in the field of quantitative GD analysis outperforms the other ones. In addition, using this approach we were able to estimate the scores with MAE = 0.65 and MAE = 0.66, respectively. If we take into account that the range of the first scale is 4, and of the second one 3, the error can be considered as very low. In fact, when assessing GD in children, psychologists tend to make the error even higher, e. g. two experts can frequently differ by 1 point (compare it to 0.65 or 0.66).

VIII.5 Conclusion

To the best of our knowledge, this is a unique study that performs an investigation of the various FD approaches in the computerized assessment of the GD in school-aged children. Therefore, it should be considered as being rather exploratory and pilot in nature. We can conclude that the employment of various FD approximations brings major differences in kinematic handwriting features. In the scope of the correlation analysis associated with the overall score, the Caputo's FD approach exceeds the rest of the analysed FD approximations. However, in the scope of the sub-score, the Riemann-Liouville gained the most significant features. Moreover, the results of the multivariate analysis suggest that the Riemann-Liouville's approximation in the field of the quantitative GD analysis outperforms the other ones (MAE = 0.65 for overall score and MAE = 0.66 for sub-score).

This study has several limitations and possible parts, that could be further improved. First of all, the dataset is relatively small in terms of the statistical validity of the results. To generalize the results, the larger dataset have to be acquired and more handwriting tasks should be included in the analysis. Next, a more granular FD α order search (step of 0.01 or even less) in order to find the optimal α range should be performed. Moreover, other feature types, such as temporal, spatial, and dynamic, should be included in future comparisons. The future study should be detailly focused on the comparison of the FD-based features with the conventionally used handwriting features. The different handwriting tasks have to be investigated separately for the best performing FD-based features. Besides, when comparing the several feature sets performance (regression, etc.) an ANOVA test should be performed in the future to analyze the differences between them. Finally, various machine learning models should be trained and compared in the future studies to get more information about the classification performance of the proposed features and to obtain the most robust models for GD identification.

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Appendix

Curriculum Vitæ

Ján Mucha

PhD student @ Brno University of Technology
Data Scientist @ Inventurist.ai

Main research interests

Non-invasive, quantitative and objective analysis of brain diseases
Fractional order derivatives and its application in signal processing

Personal

Residence	Brno, Czech Republic
Languages	Native in Slovak & Czech, Fluent in English
Contact	jan.mucha@vut.cz

Education

2016–*	PhD in Signal Processing, FEEC, BUT (expected in Q1/2021)
2014–2016	Master of Communications and Informatics, FEEC, BUT

Work experience

2016–*	Researcher at Brain Diseases Analysis Laboratory, BUT, Czech Republic
2019–*	Data Scientist at Inventurist.ai, San Francisco, USA
2018–2019	Visiting Researcher at TecnoCampus Mataró, Pompeu Fabra University, Barcelona. Spain
2015–2018	Software Developer at iXperta, Brno, Czech Repulic

Skills

Python, C++, C#, Matlab, Perl, Bash, Airflow, AWS, GCP, Signal Processing, Machine Learning, Docker, Linux, LaTeX, JavaScript, HTML

Teaching

2020–2021	Assistant lecturer: Digital signal processing
2016–2017	Assistant lecturer: Object-oriented programming in C#
2016–2017	Assistant lecturer: Signals and systems analysis
2016–2017	Assistant lecturer: Digital signal processing
2020	Bachelor thesis advisor: Marek Fiala, Web application for online handwriting acquisition by digitizing tablet
2019	Bachelor thesis advisor: Tomáš Piovarcsy, Graphic tasks dataset for personal identification
2017	Bachelor thesis advisor: Joy Tomáš Sarker, Android application for dysarthria examination using 3F test

Participation in projects

2020–2023	Technology Agency of the Czech Republic (TL03000287): Software for advanced diagnosis of graphomotor disabilities
2020–2023	Ministry of Health of Czech Republic (NU20-04-00294): Diagnostics of Lewy body diseases in the prodromal stage based on multimodal data analysis
2020–2021	Brno University of Technology (CEITEC VUT/FEKT-J-20-6146): Development of Automatic Quantitative SEM Image Analysis Method of Interconnected Porous Structure of Freeze-dried Biopolymeric Scaffolds Applicable in Tissue Engineering
2020–2022	Brno University of Technology (FEKT-S-20-6291): Multimodal analysis of audio and image signals using sophisticated signal processing methods and machine learning.
2019–2022	Ministry of Industry and Trade of the Czech Republic (FV40309): Monitoring, search, detection, guidance and tracking using video from drone–vision system for defense systems and public security forces
2018–2020	Czech Science Foundation (GA18-16835S): Research of advanced developmental dysgraphia diagnosis and rating methods based on quantitative analysis of online handwriting and drawing
2018–2019	Czech Ministry of Education, Youth And Sports (CZ.02.2.69/0.0/0.0/16_027/0008371): International mobility of researchers

2017–2021	The Marie Skłodowska-Curie Action (734718 (CoBeN)): Novel Network-Based Approaches for Studying Cognitive Dysfunction in Behavioral Neurology
2017–2019	Brno University of Technology (FEKT-S-17-4476): Multimodal processing of unstructured data using machine learning and sophisticated methods of signal and image analysis
2016–2020	European Cooperation in Science and Technology (CA15225): Fractional-order systems; analysis, synthesis and their importance for future design
2016–2019	Ministry of Health of Czech Republic (NV16-30805A): Effects of non-invasive brain stimulation on hypokinetic dysarthria, micrographia, and brain plasticity in patients with Parkinson's disease
2015–2019	Czech Ministry of Education, Youth And Sports of Czech Republic (LO1401): Interdisciplinary research of wireless technologies (INWITE)

Internships

2018–2019	TecnoCampus Mataró, Pompeu Fabra University, Barcelona, Spain
2017	TecnoCampus Mataró, Pompeu Fabra University, Barcelona, Spain

Training Schools

2018	Advantages of the fractional models in dealing with real world problem, Istanbul Gelisim University, Turkey

Awards

2017	First place at student conference EEICT 2017, FEEC, Brno
2016	Finalist of the Brno Ph.D. Talent 2017, holder of the micro-scholarship
2014	Dean award for excellent theoretical and practical knowledge during the bachelor thesis defense

Publications in journals with impact factor

2020	Mucha, J; Galaz, Z; Mekyska, J; Faundez-Zanuy; Zvoncak, V; Safarova, K; Urbanek T; Havigerova, J,M; Bednarova, J; M,Smekal, Z; 2020: Analysis of Various Fractional Order Derivatives Approaches in Assessment of Graphomotor Difficulties. IEEE ACCESS, submitted.
2020	Galaz, Z; Mucha, J; Zvoncak, V; Mekyska, J; Smekal, Z; Safarova, K; Ondrackova, A; Urbanek T; Havigerova, J,M; Bednarova, J; Faundez-Zanuy, M, 2020: Advanced Parametrization of Graphomotor Difficulties in School-aged Children. IEEE Access, vol. 8, pp. 112883-112897, 2020, doi: 10.1109/ACCESS.2020.3003214.
2019	Brabenec, L; Klobusiakova, P; Barton, M; Mekyska, J; Galaz, Z; Zvoncak, V; Kiska, T; Mucha, J; Smekal, Z; Kostalova, M; Rektorova, I, 2019: Non-invasive stimulation of the auditory feedback area for improved articulation in Parkinson's disease. PARKINSONISM & RELATED DISORDERS 61, p. 187–192, doi: 10.1016/j.parkreldis.2018.10.011
2019	Mucha, J; Mekyska, J; Galaz, Z; Faundez-Zanuy, M; Lopez-de-Ipina, K; Zvoncak, V; Kiska, T; Smekal, Z; Brabenec, L; Rektorova, I, 2018: Identification and Monitoring of Parkinson's Disease Dysgraphia Based on Fractional-Order Derivatives of Online Handwriting. APPLIED SCIENCES-BASEL 8(12), doi: 10.3390/app8122566
2019	Galaz, Z; Mekyska, J; Zvoncak, V; Mucha, J; Kiska, T; Smekal, Z; Eliasova, I; Mrackova, M; Kostalova, M; Rektorova, I; Faundez-Zanuy, M; Alonso-Hernandez, JB; Gomez-Vilda, P, 2018: Changes in Phonation and Their Relations with Progress of Parkinson's Disease. APPLIED SCIENCES-BASEL 8(12), doi: 10.3390/app8122339
2018	Mekyska, J; Galaz, Z; Kiska, T; Zvoncak, V; Mucha, J; Smekal, Z; Eliasova, I; Kostalova, M; Mrackova, M; Fiedorova, D; Faundez-Zanuy, M; Sole-Casals, J; Gomez-Vilda, P; Rektorova, I, 2018: Quantitative Analysis of Relationship Between Hypokinetic Dysarthria and the Freezing of Gait in Parkinson's Disease. COGNITIVE COMPUTATION 10(6), p. 1006–1018, doi: 10.1007/s12559-018-9575-8

2017	Brabenec, L; Mekyska, J; Galaz, Z; Zvoncak, V; Kiska, T; Mucha, J; Smekal, Z; Kostalova, M; Rektorova, I, 2017: Effects of non-invasive brain stimulation of the superior temporal gyrus on motor speech disorder in Parkinson's disease. EUROPEAN JOURNAL OF NEUROLOGY 24, p. 478–478

Publications in journals without impact factor

2019	Zvoncak, V.; Mekyska, J.; Safarova, K.; Mucha, J.; Kiska, T.; Losenicka, B.; Cechova, B.; Francova, P.; Smekal, Z. Vliv intra-writer normalizace na diagnózu vývojové dysgrafie založené na kvantitativní analýze online písma. ELEKTROREVUE–Internetový časopis (http://www.elektrorevue.cz), 2019, vol. 20, no. 6, p. 1-5. ISSN: 1213-1539.
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2017	Mucha, J.; Galaz, Z.; Smekal, Z. Detekcia Parkinsonovej choroby pomocou akustickej analýzy prednesu básne. ELEKTROREVUE–Internetový časopis (http://www.elektrorevue.cz), 2017, vol. 19, no. 2, p. 1-7. ISSN: 1213-1539.
2017	Galaz, Z.; Zvoncak, V.; Kiska, T.; Mucha, J.; Smekal, Z. Objektivní hodnocení poruch chůze na základě akustické analýzy četby dlouhého textu u pacientů s idiopatickou Parkinsonovou nemocí. ELEKTROREVUE–Internetový časopis (http://www.elektrorevue.cz), 2017, vol. 19, no. 4, p. 1-7. ISSN: 1213-1539.

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